VOLUME 80 • SEPTEMBER 1958 • NUMBER 3

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Neurochemistry and Therapeutic Endeavor
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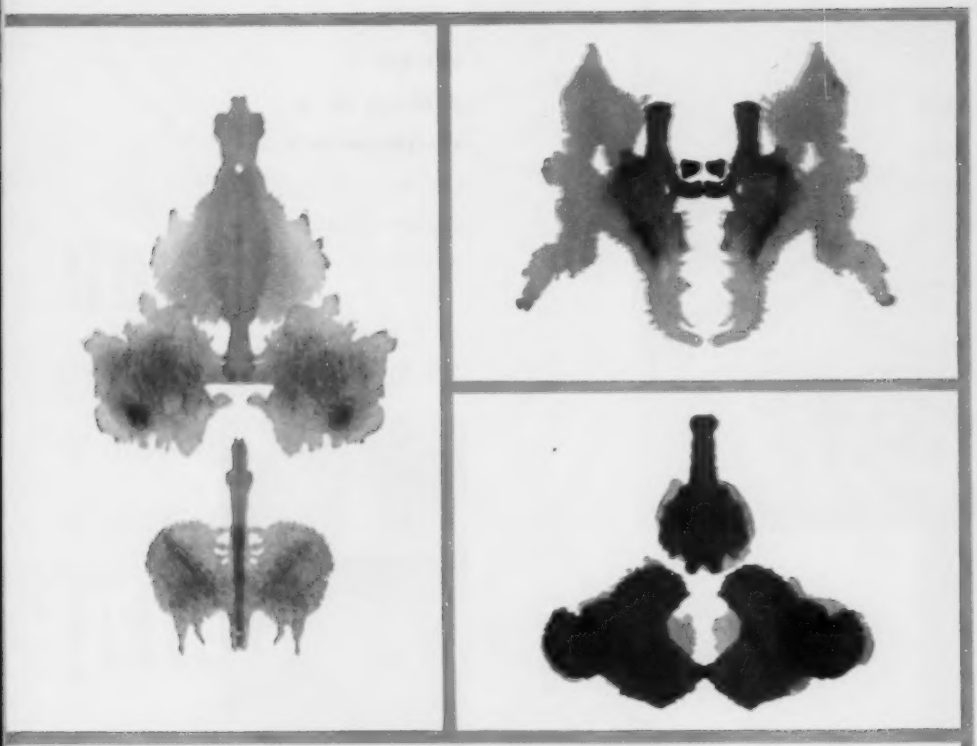

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1. Bowes, H. A.: Am. J. Psychiat. *113*:530 (Dec.) 1956.
2. Bruckman, N., *et al.*: Am. J. Psychiat. *114*:262 (Oct.) 1957.
3. MacGregor, J. M.: South African M. J. *30*:1108 (Nov. 17) 1956. 4. Sarwer-Foner, G. J., and Koranyi, E. K.: Canad. M. A. J. *77*:450 (Sept. 1) 1957.

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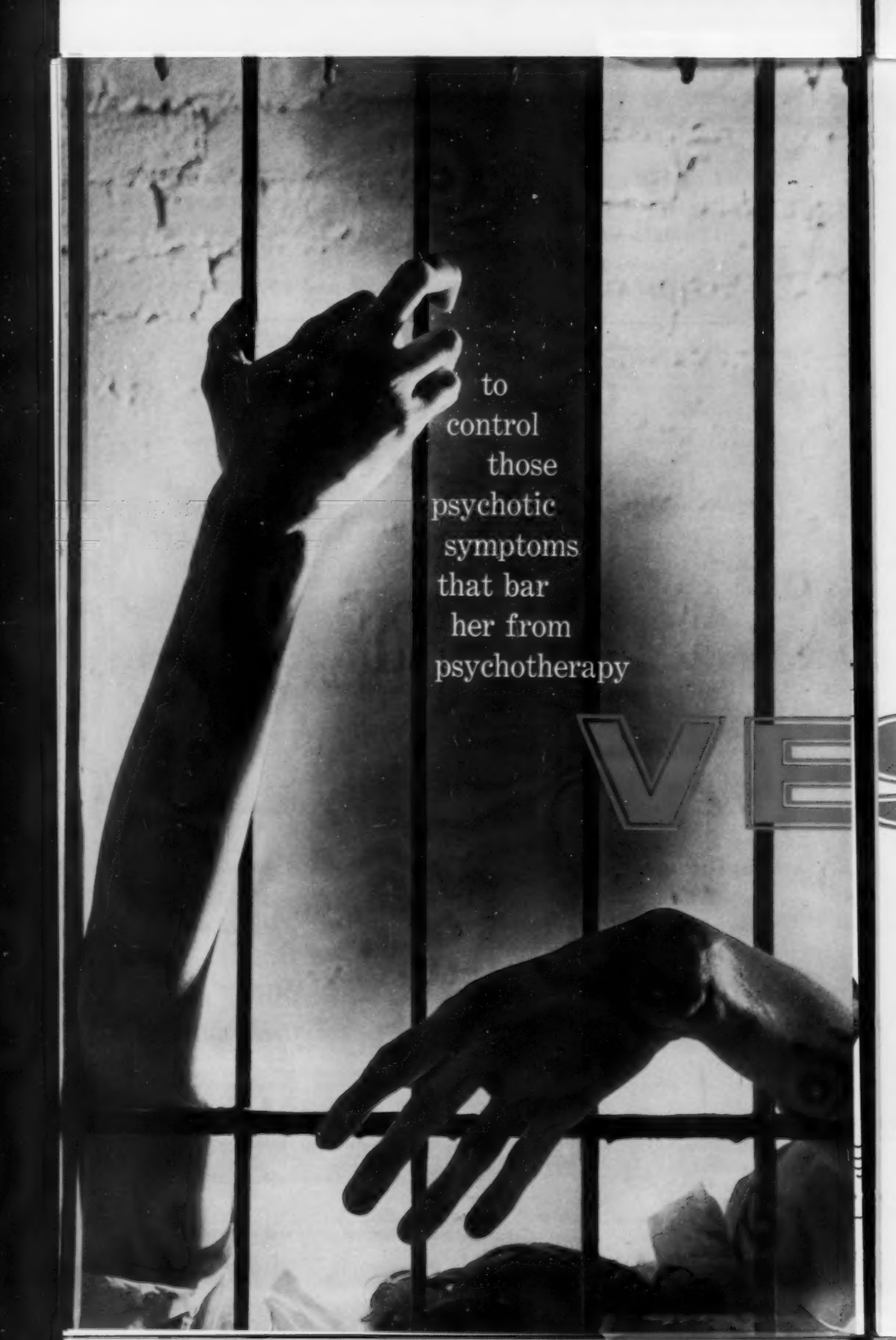
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DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
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Abnormalities in Central Regulation of Respiration in Acute and Convalescent Poliomyelitis

FRED PLUM, M.D., and AUGUST G. SWANSON, M.D., Seattle

Clinical differences between the respiratory disturbances resulting from spinal cord involvement and the breathing defects produced by brain stem lesions have been recognized in poliomyelitis for over 50 years. Despite this long recognition, there have been comparatively few detailed studies of the mode of development, frequency, or pathological physiology of "central respiratory failure" in poliomyelitis.

The earliest reference to supraspinal lesions causing respiratory difficulties in poliomyelitis appears to have been that of Wickman,[1] who stated in 1905 that respiratory paralysis could result from involvement of either "the center for the intercostal muscles" or "the nucleus of the pneumogastric nerve." Petrén and Ehrenberg,[2] in 1909, more correctly designated "the bulbar center for respiration" as the source of supraspinal respiratory defects in poliomyelitis. Subsequently, a number of authors made direct or passing reference to shallow, irregular breathing with marked variation in rate and depth as characteristic of central respiratory failure. Pathological studies, particularly by Baker and co-workers,[3,4] confirmed the belief that patients who showed this type of respiratory defect suffered major damage in the lateral medullary reticular formation. As a matter of fact, damage to the medullary reticular formation has been so common a finding in patients dying of poliomyelitis[5-7] that it is surprising that centrogenic respiratory abnormalities have not been more frequently noted as a clinical problem.

Quantitative measurements of the defect in respiratory regulation which occurs in acute bulbar poliomyelitis are limited to Sarnoff, Whittenberger, and Affeldt's observations.[8] Sarnoff et al. presented clinical, pneumotachographic, and blood gas observations on four subjects with central respiratory failure. Retention of carbon dioxide without dyspnea, correction of hypoventilation upon command, and reduction of ventilation on oxygen therapy were demonstrated. It was advanced that bulbar poliomyelitis produced three defects in respiration: (1) irregularity in rate and depth; (2) incoordination of respiratory muscles, and (3) reduction in sensitivity to carbon dioxide as a respiratory stimulus. The frequency of these defects in bulbar poliomyelitis was not presented, and little comment was made on the physiological implications of correction of hypoventilation upon arousal and command.

The present report details the clinical and physiological findings on 20 patients

Received for publication May 4, 1957.

From the Division of Neurology, Department of Medicine, University of Washington School of Medicine.

Aided by an annual grant from the National Foundation for Infantile Paralysis, Inc., to the Northwest Respirator and Rehabilitation Center, and the State of Washington Initiative 171 Funds.

who developed centrogenic respiratory disturbances due to acute poliomyelitis. Pathological material was available for correlation in two of these subjects. In addition, abnormalities are described in the central control of respiration which persisted beyond the acute phase of illness, to produce problems in the management of convalescence. These physiological defects in respiration which appear during both acute and convalescent stages of poliomyelitis appear to have relevance in evaluating current theories of the neurogenesis of normal human respiration.

Material and Methods

Patients with acute central respiratory failure were studied in the wards of the King County Hospital, Seattle, and the Providence Hospital, Anchorage, Alaska. Patients with respiratory insufficiency convalescing from poliomyelitis were studied in the Northwest Respirator and Rehabilitation Center. The entire brain was obtained for pathological study from one of the subjects observed in Anchorage, and brain tissue blocks on another patient were sent us by Dr. James W. Stephens, of the University of Colorado Medical Center.

Patients with cranial nerve paralyses or respiratory difficulties not explained by involvement of spinal motoneurons or airway obstruction were selected for study from over 250 admissions with acute poliomyelitis from 1954 to 1956, inclusive. Control studies were performed on healthy medical and nursing students, as well as on patients with spinal and nonparalytic poliomyelitis. (The patients with the clinical diagnosis of nonparalytic poliomyelitis had virus isolated from the stools.) All patients had frequent clinical examinations, and the vital capacity was measured twice daily during their acute illness. Additional studies were performed on selected patients. Respiratory patterns were monitored by a comfortably fitting chest band to which was attached a strain gauge connected with an oscillograph, shielded from the patient's view (inspiration reads up on all tracings in the illustrations). The vital capacity (VC) and maximal breathing capacity (MBC) were measured with a 9-liter Benedict-Roth spirometer with valves and CO_2 absorber removed by the technique described by Baldwin et al.[9] The predicted normal VC and MBC were calculated from the formulae of the same authors.[9] The partial pressure of carbon dioxide in alveolar air (PA_{CO_2}) was measured with an instantaneous, continuously recording infrared gas analyzer (Liston-Becker). End-expiratory and forced-expiratory samples were obtained at either the nares or the orifice of a tracheotomy tube. The arterial carbon dioxide content and oxygen saturation were determined by the manometric method of Neill and Van Slyke.[10] The arterial pH was measured with a Cambridge Research Model glass-electrode pH meter. The partial pressure of carbon dioxide in arterial blood (PA_{CO_2}) was calculated from the nomograph of Singer and Hastings.[11] Alveolar and arterial P_{CO_2} values corresponded within a range of 2 to 5 mm. Hg, the alveolar always being the lower of the two. The respiratory response to oxygen and to carbon dioxide was determined by a modification of the technique described by Nielsen.[12] Air, 100% oxygen, and quantitatively analyzed mixtures of 3%, 5%, and 6% CO_2 in air, respectively, were breathed for successive 20-minute periods from a Tissot balanced spirometer. Minute ventilation was recorded for the last five minutes of each period, and the PA_{CO_2} was monitored continuously by sampling the expired air at the mouthpiece. Minute alveolar volume was calculated by subtracting the dead-space ventilation, assuming 130 cc. for female and 150 cc. for male subjects plus 55 cc. for the valve. To graph the respiratory response to CO_2, the increase in minute ventilation was plotted as a multiple of resting ventilation (V/R) on the ordinate, and the increase in PA_{CO_2}, in millimeters of mercury, was plotted on the abscissa.

Results

Observations During Acute Poliomyelitis

The pattern of development and progression of centrogenic respiratory decompensation in acute poliomyelitis was similar in most patients and could be divided into three stages. In Stage I, respiratory irregularity appeared only during sleep and was unnoticed by the patient. Stage II was marked by more serious physiological defects in respiration, which persisted during waking hours. Effort or concentration was required to maintain compensation for oxygen and carbon dioxide. Stage III was that of respiratory decompensation; hypoxia or hypercapnia rapidly appeared unless artificial respiration was started. The clinical and physiological observations made during these three stages are detailed below.

Centrogenic respiratory abnormalities were observed in 20 patients. The major associated clinical findings in these subjects

are given in Table 1. Every patient had other clinical manifestations of bulbar poliomyelitis, although at times the cranial-nerve weaknesses were minimal in degree. Seven patients progressed no further than Stage I during their illness. Five subjects progressed to Stage II, and eight others advanced to Stage III. Thirty-eight patients acutely ill with respiratory failure caused by spinal paralysis were also treated during this same period of time. It is possible that some of the last group also had minor centrogenic defects which were masked by the more overwhelming problem of diaphragmatic and intercostal paralysis. In order to keep the observations as clear as possible, however, the present studies on centrally induced respiratory abnormalities were performed only on patients in whom spinal paralysis was insufficient to account for respiratory failure.

Stage I.—Derangement in central respiratory regulation developed insidiously, and patients were unaware of any breathing abnormality. Breathing patterns were normal during wakefulness, but irregularity in rate and depth, with periods of apnea lasting from 4 to 12 seconds, appeared during drowsiness or sleep (Fig. 1). Arousal promptly eliminated the abnormal patterns. Because of this disappearance of irregularity after arousal, respiratory difficulties were not apparent during ward rounds, direct examination, or vital-capacity testing. Alveolar P_{CO_2} determinations were normal during both waking and sleeping hours, and ventilation remained unchanged with oxygen therapy. Four of the seven patients who remained in Stage I throughout illness experienced no serious impairment of swallowing. All seven subjects were free of airway obstruction.

Respiratory irregularities were frequent in bulbar poliomyelitis. Of 15 consecutively studied patients with cranial-nerve paralyses, 7 showed decided irregularities of sleeping respiratory rhythm, with restoration of regularity upon awakening. Of 12 consecutive patients with spinal or nonparalytic poliomyelitis, 3 evinced some minor variation in rate and depth of breathing during sleep. These latter changes were not considered significant.

Stage II.—The persistence of irregular breathing during wakefulness marked progression into Stage II. Patients were conscious of irregular breathing, and several complained that they had to concentrate continuously on breathing. Concentration of effort restored regularity, at least transiently (Fig. 2*A* and *B*). Vital capacities at this stage were recorded at levels ordinarily considered adequate to maintain physiological ventilation (Table 1). Repeated pinching of the Achilles tendon or repeated commands to breathe resulted in regular respiration for the duration of the external stimuli and for several cycles beyond (Fig. 2*C*). Sleep produced a more marked degree of respiratory irregularity, with longer periods of apnea, than was seen in Stage I, so that several patients were afraid to attempt sleep. Breathing ceased altogether when one man was induced to try sleeping under supervision (Fig. 3). Although most of the patients were apprehensive about their breathing defect and their need to drive respiration consciously, dyspnea, or air hunger, was usually absent as a specific sensation.

Five patients in Stage II who were given oxygen therapy manifested hyposensitivity to carbon dioxide as a respiratory stimulus. A prompt rise in PA_{CO_2}, from resting levels of 32-41 mm. Hg to levels of from 45-54 mm. Hg was observed within minutes of starting oxygen in these subjects (Fig. 4). This depression of ventilation with oxygen therapy was not universally searched for, since oxygen usually was withheld from the treatment program of nonrespirator patients.

Drugs which depress the brain stem worsened the clinical status of patients with centrogenic respiratory disturbances. Reserpine markedly accentuated the respiratory irregularities of one woman in Stage I. A 7-year-old boy (J. B., Table 1), with swallowing paralysis but without clinically apparent respiratory insufficiency, was given

TABLE 1.—*Clinical Data in Twenty Patients*

			Extent of Paralysis			Circulation		
Name	Sex	Age	Cranial Nerve	Spinal	Swallowing Paralysis	Min. VC % Predicted	Hypertension	Hypotension	VC at time of Resp. Failure
Stage I									
E. S.	F	33	R 10 ++	±	++	65.5	None	None	No failure
B. W.	F	26	R & L 10 +	+	+	70.0	None	None	No failure
J. F.	M	28	R 7 +; R 10 +++; L 10 +; R 11 +; L 11 +	±	++++ 11 days	100.0	None	None	No failure
C. S.	F	24	R 11 +	—	±	100.0	None	None	No failure
O. P.	F	28	R 7 +; 10 ++; R & L 11 +	—	++++ 4 days	58.0	None	None	No failure
M. D.	F	21	L 7 & 10 +++; R 11 ++	±	++++ 2 days	75.8	None	None	No failure
J. E.	M	29	R 7 & 10 +; R & L 11 +	—	+	90.0	None	None	No failure
Stage II									
R. R.	M	28	0	+	—	12.6	135/95	None	26.4%
R. F.	M	32	R & L 10 +; R & L 11 +++	++	++++ 14 days	11.2	150/90	None	56.2%
R. S.	M	34	R & L 10 ++	+++	++++	22.9	200/100	None	22.9%
G. L.	M	23	R 7 +++; R & L 10 +++; R & L 11 ++	+++	++++	21.0	170/100	None	42%
J. C.	F	4	R & L 10; R 7	+	+++	40.0	None	80/?	40%
Stage III									
J. S.	M	26	R & L 7 +; R & L 10 +++; R & L 11 +	++	++++	Not measuerd	++	None	Not measured
J. B.	M	7	R & L 10 +++	++	++++	Not measured	None	+++; Blood & vasopressors	Not measured
D. D.	M	23	R & L 5, 7, 9, 10, 11, 12	++	++++	62.6 before apnea	160/80	++++ Blood & vasopressors	62.6%
P. G.	F	36	R & L 3, 4, 6, 7, 9, 10, 11, 12 ++++	+	++++	—	None	++++ Cardiac arrest	44%
A. W.	M	32	R & L 10 ++	++	++++	11	None	++++ Vasopressors	48%
F. L.	M	19	R 5 ++; L 7 ++; R & L 10, 11, 12 +++	++	++++	8	150/75	++++ Blood & vasopressors	55%
P. D.	M	6	R & L 10 +++	+	++	—	148/88	++++ Vasopressors	40%
V. J.	M	5	R & L 10, 11 +++	+	+++	Not measured	130/?	None	Not measured

intravenous thiopental anesthesia for tracheotomy. He remained in coma postoperatively, and his serum bicarbonate rose to 34 mEq. per liter, providing indirect evidence of abnormal CO_2 retention. He was placed on artificial respiration and was unable to initiate any spontaneous breathing for the next eight days, after which he rapidly and completely recovered without respiratory paralytic residua. A 26-year-old man (J. S., Table 1), with mild respiratory irregularity but no severe respiratory difficulties, was given 50 mg. of meperidine hydrochloride (Demerol) to allay his apprehension. Within 30 minutes, long periods of apnea and cyanosis ap-

with Acute and Convalescent Poliomyelitis

Treatment			
Art. Resp., Duration	Recovery VC	Tracheotomy	Manifestations
None	78.7%	None	Irregularity in rate and depth when drowsing, with apneic periods of 12 sec.
None	70%	None	Irregularity in rate and depth when drowsing, with apneic periods of 4 sec.
None	100%	None	Irregularity in rate and depth when drowsing, with apneic periods of 6 sec.
None	100%	None	Irregularity in rate and depth when drowsing, with apneic periods of 7 sec.
None	65.2%	None	Irregularity in rate and depth, accentuated after reserpine with apneic periods of 8 sec.
None	61.5%	None	Irregularity in rate and depth during sleep, with apneic periods of 5 sec.
None	100%	None	Irregularity in rate and depth when drowsing
Tank 10 days; rocking 12 days	104%	None	Irregularity in rate and depth when awake, completely apneic for 70 sec. during sleep
Tank 8 days; rocking 10 days	67.2%	Yes	Irregularity in rate and depth breathing; intermittent apnea; patient unable to sustain ventilation despite VC 56.2%; spinal paralysis later developed and VC dropped to 11.2%
Tank 2 wk.; rocking 60 days	76%	Yes	Irregularity in rate and depth when awake, with apneic periods of 24 sec.; only transient response to commands to breathe
Tank 8 days; rocking 21 days	68%	Yes	Rapid progression of irregular breathing, lapsing into semistupor; patient later unable to initiate sustained respirations on command when removed from tank respirator; recordable VC never less than 21%
Tank intermittent 2 days	>50%	None	Totally irregular respiratory pattern; patient unable to sleep during acute illness except in respirator, responded to command with excellent respirations
Tank 20 days; rocking 8 mo.	43%	Yes	Marked irregularity in rate and depth, with prolonged apneic periods and cyanosis after 50 mg. meperidine HCl
Tank 22 days	Not measured est. 90%	Yes	Irregularity in rate and depth, accentuated by thiopental anesthesia; CO_2 retention developed with bicarbonate of 34 mEq.; patient unable to initiate any respiratory effort for 18 days after placed in body respirator
Tank 6 days	Died	Yes	"Cogwheel" irregularity of inspiration, progressing rapidly to total irregularity and apnea, with complete inability to initiate respiratory act
Tank 12 hr.	Died	Yes	Rapid progress to total apnea with minimal spinal paralysis; gill-like breathing motions terminally
Tank 33 days rocking 120 days	46.6%	Yes	Irregularity in rate and depth and acute awareness of need to drive respiration consciously
Tank 30 days; rocking at night indef.	42.8%	Yes	Irregularity in rate and depth, progressing rapidly to ineffectual gasps; brief deep breaths on command but patient unable to maintain compensation despite VC of 55%
Tank 9 ½ hr.	Died	Yes	Child with negligible spinal paralysis, swallowing failure, given general anesthetic for tracheotomy, remained in coma; respirations irregular but intermittently deep; $P_{A}CO_2$ climbed to 52 mm. Hg; O_2 masked hypoventilation
Tank 14 days	Not measured est. 100%	Yes	No spinal paralysis; irregular breathing progressing rapidly to ineffectual respiratory efforts and stupor; incoordination between irregular breathing patterns and respirator a problem until hyperventilation was produced

peared and necessitated immediate artificial respiration. A 36-year-old woman treated in another hospital was reported to have had mild bulbar poliomyelitis, with partial swallowing paralysis and slightly irregular respirations. She was given 50 mg. of meperidine hydrochloride on the eighth day of her illness, when she was afebrile and apparently stable. Thirty minutes later she became apneic and pulseless and died.

Stage III.—In this stage respiratory homeostasis was lost. Gross irregularities in the rate and depth of breathing produced a chaotic respiratory pattern with varying periods of apnea. Some patients continued to initiate a few breaths each time they were

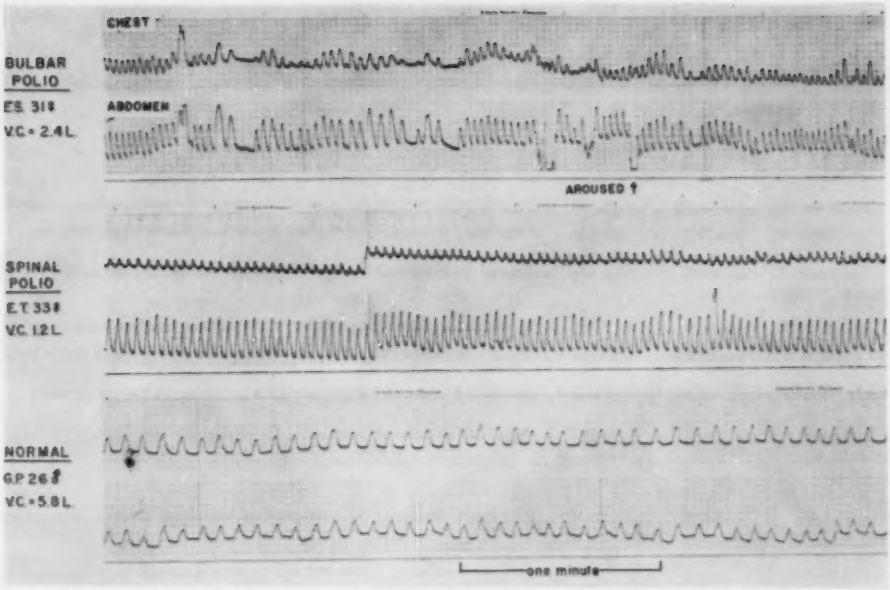
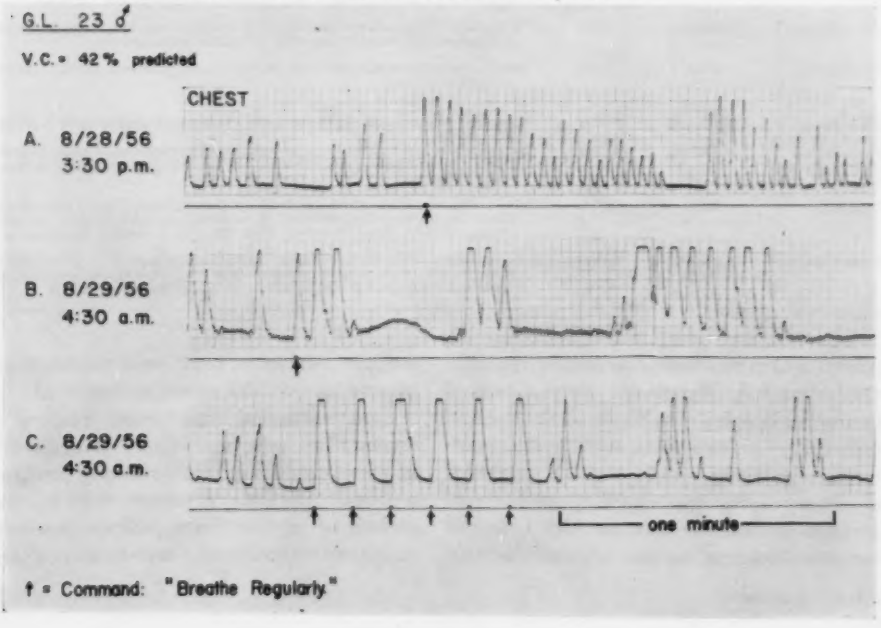


Fig. 1.—Stage I: Irregular respiration during sleep. Upper tracing (E. S. Table 1): characteristic pneumogram of Stage I of central respiratory failure in poliomyelitis. Note the irregularity in rate and depth of breathing during sleep, with improved regularity upon arousal. The middle tracing (E. T., Table 3) was taken at a time when the patient had already developed moderate diaphragmatic and intercostal paralysis but had not yet developed respiratory failure. The lower tracing (G. P.) was taken on a healthy laboratory worker during sleep.

Fig. 2.—Respiratory stimulation by command. G. L. was in the fourth day of acute bulbospinal poliomyelitis when pneumogram *A* was recorded. He had moderate weakness of the legs and swallowing paralysis but was awake and alert. At the arrow he was asked to concentrate on breathing regularly. Note the ultimate return to a totally irregular pattern.

Tracings *B* and *C* were recorded 12 hours after *A*. He had not been able to sleep. The vital capacity was unchanged, but only brief regularity in breathing followed command. In tracing *C*, repeated commands to breathe showed a 1:1 response.



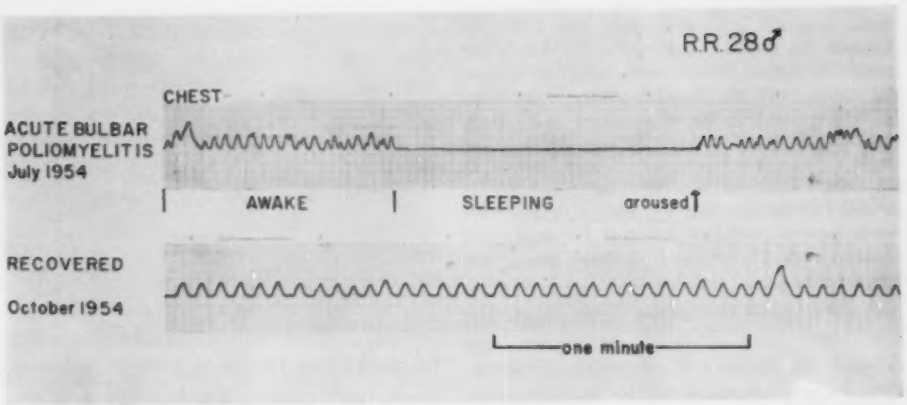


Fig. 3.—Apnea developing during sleep (Stage II). R. R. developed an irregular breathing pattern on the third day of his acute illness. The VC was 26% of the predicted normal. There were no definite cranial nerve paralyses. He spontaneously complained that he had to stay awake to keep breathing. Reassured that he would be supervised for any difficulty, he dozed (upper tracing). Apnea ensued and persisted for 75 seconds, until he was forcibly aroused by shouting. Note the lack of hyperpnea at the end of the apneic period. Completely normal ventilation was regained in convalescence (Table 3). The lower tracing demonstrates his breathing pattern three months after the acute illness.

commanded to breathe; others responded only transiently and ineffectively to commands or other external stimuli. At times, there was a complete inability to initiate any respiratory act. If artificial respiration was not started promptly, carbon dioxide retention and arterial oxygen desaturation developed rapidly and impaired consciousness.

Stage III developed precipitously in cases with fulminating disease of the brain stem or when depressant drugs were administered to patients in Stage II.

D. D., a 23-year-old man, admitted 14 hours after the onset of swallowing paralysis, had irregular respiratory efforts with an inspiratory "cogwheel" pattern on spirometric tracings. His vital capacity was 2.8 liters, and his minute volume was 7.2 liters. A tracheotomy under local anes-

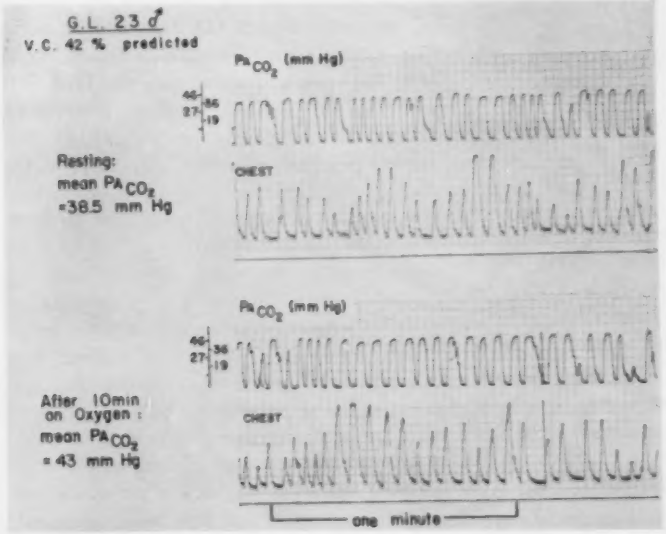


Fig. 4.—Hypoventilation with oxygen therapy. Continuous PA_{CO_2} (at the nares) and pneumogram recorded on Patient G. L. 27 hours after the tracing in Figure 2A. He had been able to sleep intermittently. The upper tracing shows his resting level of PA_{CO_2}. One hundred per cent oxygen was given by a face cone at 12 liters a minute. Note the rise in PA_{CO_2} demonstrated in the lower tracing. The patient was placed in the respirator after the above observation was made.

thesia provided a clear airway but failed to eliminate the respiratory irregularity. Within six hours respirations became more irregular in rate and depth, and the blood pressure rose from 145/80 to 168/98. He was placed in a body respirator. For a few hours he was able to make single vigorous respiratory efforts upon command, but then he lapsed into total apnea. Bilateral paralysis of the 5th, 7th, 9th, 10th, 11th, and 12th cranial nerves developed. He died five days after admission, of a perforated duodenal ulcer with hemorrhage.

A less rapid development of Stage III was seen when artificial respiration was delayed for patients in Stage II. Progressive fatigue appeared to be an important factor in the gradual loss of ability to drive respiration consciously. However, evaluation of fatigue in producing total respiratory failure was limited, as patients treated by us from the onset of their disease usually were provided with artificial respiration whenever they progressed significantly into Stage II.

Treatment.—No specific treatment was required for the breathing defect in Stage I, although the clinical symptoms alerted the staff that more serious problems might develop. It was learned that sedative or tranquilizing drugs must be avoided with acutely ill patients, and oxygen therapy could be used safely only in conjunction with artificial respiration. When general anesthesia was employed for tracheotomy, it proved necessary to follow it with artificial respiration.

Artificial respiration by tank respirator was required sooner or later to treat all 13 patients in Stage II or Stage III. Respiratory decompensation was an obvious indication for artificial respiration, but most patients were placed in the respirator before decompensation was reached. Artificial respiration was started whenever patients admitted the need to concentrate in order to breathe, when sleep had been delayed because of apprehension about breathing, or when alveolar CO_2 tensions rose above normal (40-42 mm. Hg).

Irregular central respiratory control and laryngeal incoordination sometimes produced chest motion out of phase with the respirator. This problem was overcome by eliminating glottic obstruction by tracheotomy and then increasing respirator pressures and rates to produce hyperventilation (with PA_{co_2} usually about 28 mm. Hg). Respirator pressures then were reduced gradually to maintain just enough ventilation to eliminate the endogenous respiratory drives caused by carbon dioxide.

Complete swallowing paralysis developed sooner or later in 9 of the 13 patients in Stages II and III, and all 9 of them were given tracheotomy. Tracheotomy was performed in several patients in advance of serious swallowing difficulty because artificial respiration was contemplated; with progressive bulbar disease the likelihood of eventual nucleus ambiguus involvement was great. Tracheotomy failed to eliminate abnormal centrogenic breathing patterns, although coughing, gasping, or other irregularities induced by obstructing secretions disappeared after the procedure.

Mortality and Pathology.—There were 3 deaths in the total series of 51 patients with either central or spinal respiratory failure. All three were in patients with fulminating disease of the brain stem and central respiratory failure. Autopsy was obtained on one of our own subjects (D. D.), and, in addition, examination was made of tissue blocks from the brain of another patient (H. I. S.), who suffered from central respiratory failure. This woman, a patient of Dr. James W. Stephens, died suddenly on the 20th day of her illness. The immediate cause of death was not apparent on autopsy. Dr. Stephens' notes recorded: "It was repeatedly noted that when she was taken out of the tank . . . she had a vital capacity . . . usually between 1200 and 1500 (cc.); yet when she was left alone, without any sensory stimulus given her outside the tank, her respirations became shallow and very irregular and from time to time would stop altogether for a period as long as 30 or 45 seconds, only starting again when she was told to breathe, so that repeatedly one would

Fig. 5A.—Medulla at the lower level of the inferior olive from H. I. S. Note the pale area of necrosis in the region of the left nucleus ambiguus and surrounding lateral reticular formation. This measured 3 mm. in greatest diameter.

have to stand over her counting in order to make her breathe."

Tissue blocks were taken from the brain of H. I. S. at the level of the decussation of the pyramids, at the level of the hypoglossal nucleus and inferior olive, and at the mid-pontine level. Sections were examined from D. D. at 2-3 mm. intervals from C-1 to the midbrain. Selected blocks also were prepared from other sites. Both patients showed extensive inflammation and neuronal alterations in the medullary reticular formation, particularly in the ventrolateral reticular formation, from the level of the acoustic tubercles down to the level of the pyramidal decussation. In both cases, small necrotic

Figs. 5B, 5C, and 5D.—Sections from D. D.

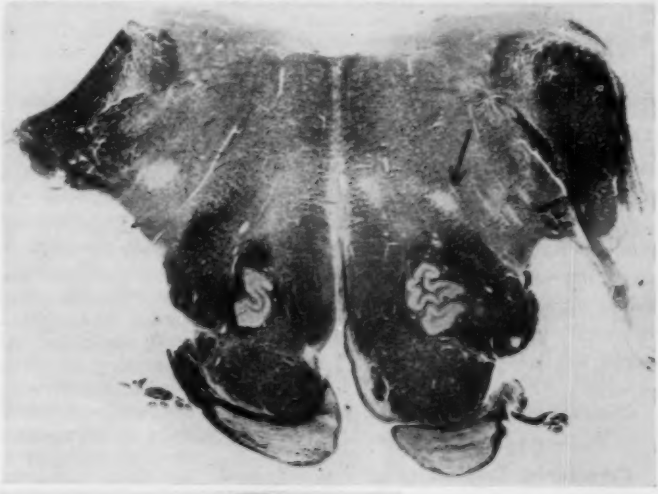


Fig. 5B.—Caudal border of pons. The area of necrosis on the left lies in the region of the nucleus of spinal V. There were several tiny areas of necrosis in the ventral reticular formation on the right, the largest of which is indicated by the arrow.

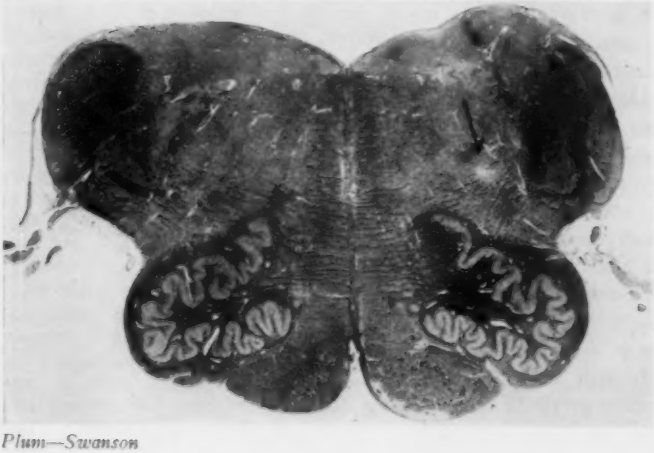


Fig. 5C.—Medulla at level of the inferior olive. The extensive inflammatory changes in the ventral lateral reticular formation extended to this section. An area of necrosis is indicated by the arrow.

Fig. 5D.—Medulla at the level of the pyramidal decussation. The necrotic focus on the right lies in the reticular formation just ventral to the descending root of spinal V.

foci of 1-2 mm. diameter were observed in the ventrolateral reticular formation (Figs. 5A-5D). At pontine levels, inflammatory changes in the reticular formation were moderately intense and consisted predominantly of perivascular infiltration with mononuclear cells without severe neuronal alteration or necrosis. D. D. also showed fairly severe inflammatory infiltration and neuronal loss in the trigeminal motor nuclei.

Observations During Convalescence from Poliomyelitis

Permanent Respiratory Irregularity and Hyposensitivity to Carbon Dioxide During Sleep.—The characteristic clinical abnormalities in respiration induced by defective central control of breathing seldom lasted more than two weeks after the end of the acute stage of poliomyelitis. However, major disturbances in central respiratory control persisted late into convalescence in at least two subjects. Both these patients progressed to Stage III failure during their acute illness, and it proved difficult during convalescence to emancipate them from respiratory aid, particularly during sleep. Physiological studies showed irregular respirations during drowsiness or sleep, retention of carbon dioxide during sleep, depression of ventilation when breathing oxygen, and a reduced response to carbon dioxide as a respiratory stimulus. Both subjects demonstrated choreiform movements involving the head and extremities during sleep.

Report of Cases

F. L., a 19-year-old youth, developed swallowing paralysis two days prior to admission, on Nov. 15, 1954. He had partial paralysis of the right 5th and left 7th and bilateral paralysis of the 10th, 11th, and 12th cranial nerves. Respiration was markedly irregular in rate and depth when he was awake, but his vital capacity was 55% of the predicted normal. During his first hospital day a tracheotomy was done, and he was placed in a body respirator because the marked respiratory irregularity threatened to produce hypoventilation. There were serious complications during the acute illness: Gastrointestinal hemorrhage necessitated transfusion with whole blood, and his blood pressure was supported with vasopressors for 96 hours (Table 1).

During the first six months of convalescence he was seriously and, at times, critically ill. Persistent swallowing paralysis with regurgitation of gastric contents made it difficult to feed him, and he had repeated episodes of pneumonitis and pyelonephritis. His vital capacity gradually increased to 1.7 liters (39% of predicted) by the sixth month, but, in order to sleep, he required respiratory aid in the form of a rocking bed. During drowsiness or sleep his respirations were irregular, and choreiform movements of the head and extremities appeared. He became progressively drowsier during the day, falling asleep when eating or during physical therapy. Residual skeletal muscle strength was sufficient to allow walking and functional use of both arms, but his progress was slow. Ten months after the acute illness, studies were performed (Table 2A) which demonstrated marked arterial hypercapnia and normal O_2 saturation. Breathing pattern is shown in Figure 6, upper tracing. He had an audible inspiratory laryngeal stridor and a diminished inspiratory flow rate. At first, airway obstruction was suspected to be the cause of his respiratory difficulty, and the tracheotomy, which had been closed during the seventh month, was reestablished. Table 2A records the data following tracheotomy. Ventilation improved, but irregular respiration (Fig. 6, middle and lower tracings) with retention of carbon dioxide persisted during sleep. His minute ventilation was reduced when he was breathing 100% oxygen. He had adequate pul-

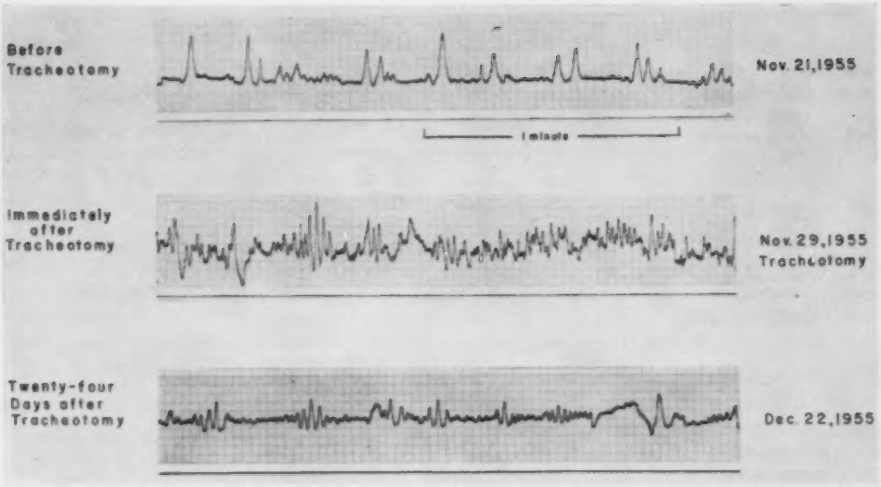


Fig. 6.—Pneumograms before and after replacement of tracheotomy in F. L. The respiratory irregularity failed to improve after the creation of an unobstructed airway.

monary reserve to overcome CO_2 retention and could ventilate voluntarily into hypocapnic ranges. The CO_2 retention and overwhelming drowsiness during the day were relieved by the tracheotomy, however, and his rehabilitation program progressed more rapidly.

A follow-up examination nine months later showed persistence of the irregular respiration and choreiform activity during sleep. Sleeping PA_{CO_2} was 53.2 mm. Hg (normal mean PA_{CO_2} during sleep=46.3 mm. Hg [13]). Numerous efforts to free him from artificial respiration at night were unsuccessful, as they induced progressive CO_2 retention without dyspnea. His ventilatory response to increased tensions of CO_2 in the inspired air was depressed markedly (Fig. 8*B*; F. L., Table 3).

A. W., a 32-year-old man, was admitted Oct. 23, 1954, with acute poliomyelitis. He complained of stiffness of his neck and a weak left arm. There were no gross cranial-nerve paralyses, but his voice had developed a nasal quality. His vital capacity was 4.2 liters (94% of the predicted normal). During his first hospital day he complained of having to concentrate on breathing, and his respirations were jerky and irregular. The vital capacity fell to 49%, and he was placed in a body respirator in order to provide rest. His disease progressed, and coma and swallowing paralysis developed. Partial obstruction of the airway by secretions ensued, although he had a tracheotomy, and arterial oxygen desaturation was present for five days during the acute illness. His blood pressure had to be supported with vasopressors for three days (Table 1).

TABLE 2.—*Ventilatory and Blood Gas Data*

	A. Patient F. L.	
	Before Tracheotomy	After Tracheotomy
Percentage predicted VC	42.8 (1.8 L.)	42.8
Percentage predicted MBC	13.9 (15.5 L/min.)	31.5 (35 L/min.)
PA_{CO_2} awake, mm. Hg	70	45.5
PA_{CO_2} with hyperventilation, mm. Hg	--	26
Pa_{CO_2} asleep, mm. Hg	71.5	55
Art. O_2 saturation	94.3%	96.4%
Arterial pH	7.39	7.40
Minute ventilation, air *	2.970 L.	4.97 L.
Minute ventilation, oxygen	2.14 L.	3.63 L.
	B. Patient A. W.	
	During Tracheobronchitis	Recovered
Percentage predicted VC	32.3 (1.4 L.)	48.6 (2.2 L.)
Percentage predicted MBC	34 (48.5 L/min.)	52 (73.5 L/min.)
PA_{CO_2} awake, mm. Hg	55.5	43.1
PA_{CO_2} with hyperventilation, mm. Hg	--	35
PA_{CO_2} asleep, mm. Hg	59.5	59.6
Arterial pH		7.40
Minute alveolar ventilation, air	--	5.10 L.
Minute alveolar ventilation, oxygen	--	3.9 L.

* Alveolar ventilation could not be calculated accurately because of respiratory irregularity.

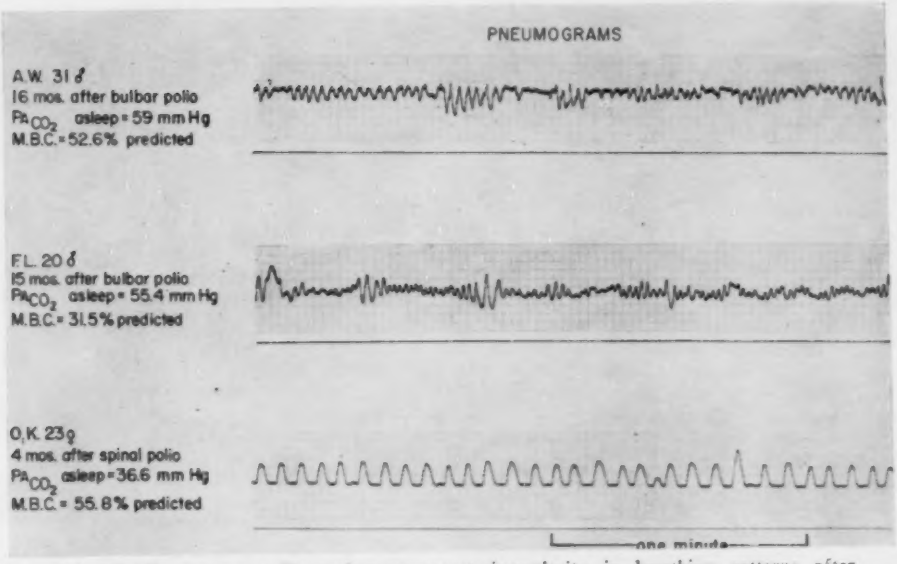

PNEUMOGRAMS
A.W. 31 ♂
16 mos. after bulbar polio
Pa_{CO_2} asleep = 59 mm Hg
M.B.C. = 52.6% predicted
F.L. 20 ♂
15 mos. after bulbar polio
Pa_{CO_2} asleep = 55.4 mm Hg
M.B.C. = 31.5% predicted
O.K. 23 ♀
4 mos. after spinal polio
Pa_{CO_2} asleep = 36.6 mm Hg
M.B.C. = 55.8% predicted
one minute

Fig. 7.—Pneumograms illustrating permanent irregularity in breathing patterns after poliomyelitis. A. W. and F. L. are reported on in the text. O. K. had spinal poliomyelitis without clinical signs of bulbar involvement. She had no respiratory irregularity during the acute phase or in convalescence. However, four months after the acute illness she had a reduced response to CO_2 as a respiratory stimulus (Fig. 8 and Table 3).

In early convalescence irregularity in rate and depth of breathing and choreiform movements of the extremities were noted during drowsiness or sleep. The vital capacity returned to 36%; but emancipation from the respirator was slow, and four months were required to eliminate nighttime respiratory aid. He was discharged seven months after admission. At that time his trunk and lower-extremity muscles were normal, but he had severe residual paralysis in his neck, shoulders, and upper extremities.

Nine months later he developed a low-grade tracheobronchitis. A chronic cough and increasing drowsiness persisted for a month before he sought medical care. He did not complain of dyspnea but had a PA_{CO_2} of 55.5 mm. Hg. Drowsiness and hypercapnia cleared after three days of artificial respiration and treatment of the tracheo-

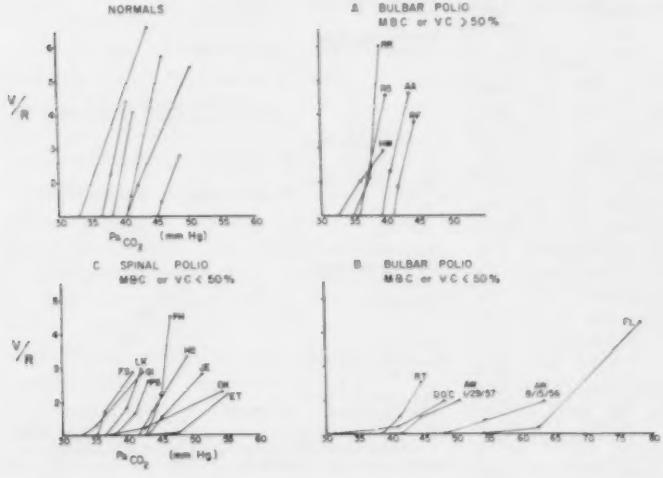


Fig. 8.—Carbon dioxide sensitivity following poliomyelitis. The ventilatory response to breathing increased concentrations of carbon dioxide. V/R = minute alveolar ventilation on CO_2 divided by resting minute alveolar ventilation.

bronchitis. Table 2B records ventilatory and blood gas data before and after treatment. The sleeping respiratory pattern was irregular in rate and depth (Fig. 7), and he had choreiform movements during sleep. Despite the respiratory abnormalities, he no longer needed a respirator once the infection was clear. He was able to reduce his PA_{CO_2} to hypocapnic ranges by voluntary overbreathing. A follow-up examination two months later revealed that the irregular breathing pattern and choreiform movements during sleep were unchanged. His sleeping PA_{CO_2} was 50.8 mm. Hg. Measurements of his ventilation while he was inhaling increased concentrations of CO_2 showed a depressed response to the CO_2 stimulus (Fig. 8), although his MBC was 51% of the predicted normal (Table 3). Oxygen breathing depressed his minute respiratory volume.

Studies were again repeated in March, 1958. Sleeping PA_{CO_2} was 57 mm. Hg, and he was repeatedly awakening from sleep, feeling frightened but not dyspneic. Because of these findings the patient has been provided permanently with a rocking bed for sleep. This has eliminated both the nocturnal awakening and the elevated PA_{CO_2}.

Ventilatory Response to Carbon Dioxide Following Poliomyelitis

After the reduced ventilatory response to carbon dioxide was observed in the two patients described above, CO_2 response curves and the ventilatory response to oxygen were determined on a group of 16 additional adult patients convalescing from poliomyelitis. The patients were divided into three groups. All had required respirators during acute poliomyelitis and were studied several months after the end of acute disease. Group A had Stage II or Stage III centrogenic respiratory failure during acute poliomyelitis but had shown good to excellent recovery at the time of study. Vital capacity and maximal breathing capacity values were over 50% of the predicted normal. Group B had both bulbar and spinal paralysis during acute poliomyelitis. At the time of study, moderate to severe residual spinal respiratory paralysis remained, with the VC or MBC less than 50% of the predicted normal. Group C had no evidence of central respiratory defects or cranial nerve paralysis during acute illness; the patients suffered moderate to severe residual paralysis of the diaphragm and intercostal muscles, with an MBC or VC of less than 50% of the predicted normal. Only E. T. still required artificial respiration. Patients with overwhelming residual paralysis showing either a MBC or a VC of less than 25% were not included in either Group B or Group C. This ex-

TABLE 3.—*Ventilatory Response to Oxygen and Carbon Dioxide*

Name	Age	Sex	% Predicted MBC	% Predicted VC	PA_{CO_2} Values, Mm. Hg At V/R=1	PA_{CO_2} Values, Mm. Hg At V/R=2	PA_{CO_2} Values, Mm. Hg Difference	Minute Alveolar Volume, Liters Air	Minute Alveolar Volume, Liters Oxygen	Minute Alveolar Volume, Liters % Change
Group A										
A. A.	22	F	52	50	39.1	40.5	1.4	5.40	6.00	+11.1
R. F.	33	M	54	80	41	42.2	1.2	5.13	5.13	0.0
R. R.	31	M	120	110	35	37.3	2.3	4.49	5.12	+14.0
R. S.	37	M	65	76	35.7	36.7	1.0	4.85	4.55	— 6.2
H. W.	38	F	110	75	32.5	36	3.5	5.34	5.45	+ 2.1
					Mean difference±S. E.		1.88±0.37		Mean change	+ 4.2%
Group B										
D. O'C.	30	M	39	45	31.5	47.7	16.2	8.24	--	--
R. T.	16	M	25	66	38.6	42.8	4.2	5.63	4.85	—13.9
A. W. 8/15/56	34	M	51	48	48.2	63.5	15.3	4.44	3.18	—28.4
A. W. 1/29/57	34	M	47	44	41.5	50.3	9.8	5.15	4.06	—21.2
F. L. 12/13/55	22	M	32	43	45.5	56.5	14	4.97 *	3.63 *	—27.0
F. L. 8/15/56	22	M	32	37	54.2	66.7	12.5	4.34 *	--	--
					Mean difference±S. E.		12.0±1.79		Mean change	—22.6%
Group C										
F. S.	29	F	45	52	35.2	37.0	1.8	4.86	5.06	+ 4.2
L. K.	34	F	34	62	36.2	40.1	3.9	3.88	3.68	— 5.3
G. I.	30	F	52	49	33.2	37.8	4.6	4.94	5.05	+ 2.2
P. S.	22	F	29	20	37.8	41.8	4.0	5.83	5.41	— 7.2
P. H.	15	F	44	36	42.7	44.6	1.9	3.81	3.41	—10.5
H. S.	37	M	26	24	41.4	44.5	3.1	3.45	3.82	+10.7
J. E.	16	M	26	25	42.7	46.4	3.7	6.12	--	--
O. K.	25	F	62	47	36.6	50.0	13.4	5.77	--	--
E. T.	33	F	37	27	43.2	53.1	9.9	3.62	--	--
					Mean difference±S. E.		5.14±1.36		Mean change	—1%

* Total minute ventilation.

clusion was made in order to prevent, as much as possible, factors of restricted chest motion and fatigue from affecting the CO_2 response. At the time of study no patient was systemically ill, and no patient had parenchymal disease of the lungs.

Figure 8 and Table 3 show the ventilatory response to inhaled carbon dioxide of healthy adults studied in this laboratory, as well as the responses of the three groups convalescing from poliomyelitis. In the normal subjects a mean rise in PA_{CO_2} of 1.67 mm. Hg (range 1.5-2.0 mm. Hg) was required to double the ventilation over resting levels. This corresponds closely with Peabody's [14] and Tenney's [15] findings for normals. In Group A, a mean rise in PA_{CO_2} of 1.88 ± 0.37 mm. Hg resulted in doubling the ventilation. Only H. W.'s values fell significantly outside the normal range. In Group B, a mean rise in PA_{CO_2} of 12.0 ± 1.70 mm. Hg was required to double the ventilation. No patient in Group B fell within the normal range. In Group C, a mean rise in PA_{CO_2} of 5.14 ± 1.36 mm. Hg was required to double the ventilation over resting levels. Although the rise in PA_{CO_2} associated with doubling ventilation over resting levels was usually less marked in this group than among patients in Group B, only two patients in Group C had responses which were within the normal range.

The ventilatory response to oxygen was determined in all patients in Group A, in three patients in Group B, and in six patients in Group C. The difference in response to oxygen between subjects in Group A and subjects in Group C was not significant, and no patient in these groups had the minute ventilation reduced more than 10.5% while breathing oxygen. Both A. W. and F. L. in Group B, however, showed a decrease in minute ventilation of more than 20% while breathing oxygen.

Review of the clinical data and ventilatory capacity of the subjects in Groups B and C who showed varying degrees of CO_2 responsiveness evinced no consistent differences in severity of acute illness,

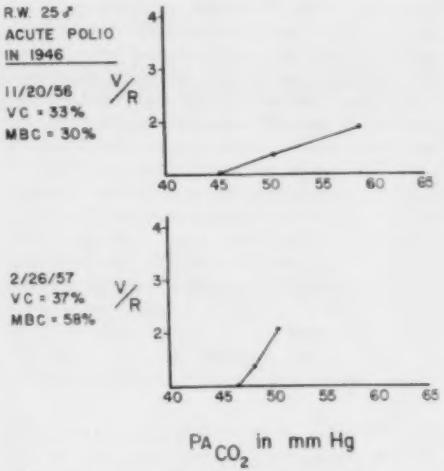


Fig. 9.—Effect of an improved MBC on the ventilatory response to carbon dioxide.

"encephalitic" symptoms, pulmonary complications, or other clinical findings. Within each group there was no correlation between the CO_2 response curves and the extent of ventilatory return. All the patients were able to hyperventilate voluntarily to levels considerably in excess of the minute volumes obtained by determining CO_2 responsiveness. The two patients with the lowest responsiveness, O. K., in Group C, and A. W., in Group B, had the highest MBC values of their respective groups.

Although CO_2 responsiveness could not be correlated with the return of ventilatory function, when one patient was compared with another, there was evidence that factors outside the nervous system affected the response to CO_2. Figure 9 illustrates the ventilatory response to CO_2 of R. W., a 25-year-old man, who had severe spinal poliomyelitis in 1946. He had not needed respiratory aid from 1947 until October, 1956, when he had severe bronchopneumonia, with marked carbon dioxide retention and respiratory acidosis. This required two weeks of treatment in a respirator for correction. On Nov. 20, one month after this illness, he doubled his ventilation only after a rise in PA_{CO_2} of 15 mm. Hg. His MBC at this time was 30%; his VC, 33%. Three

months later his MBC had increased to 58% of the predicted normal level and his VC to 37%. He doubled his ventilation, with a rise in PA_{CO_2} of 4 mm. Hg.

Comment

These observations outline a progressive physiological abnormality in the control of respiration resulting from bulbar poliomyelitis. Respiratory rhythmicity is first impaired, but, in its early stages, dysrhythmia appears only during sleep, when afferent neural stimuli and the activity of the rostral reticular formation are markedly reduced. As the lesion progresses, loss of rhythm persists into waking hours, and increased neural activation by conscious effort or by auditory or painful stimuli is required to restore regularity. Impairment of chemosensitivity of the respiratory centers at this stage is strongly suggested by reduction in ventilation and induction of CO_2 retention by oxygen therapy.[16,17] Further progression of the disease produces a state in which an increasing amount of neural stimulation must be recruited to produce ventilatory efforts. Finally, reflex responsiveness of the respiratory center is lost, and sustained ventilation will not follow any stimulus. At any of the above stages of progressive failure, depressant drugs rapidly accelerate the deterioration of respiratory control.

There are two major theories of the neurogenesis of respiration. The first, summarized by Pitts,[18] views the medullary respiratory center as tonically active in inspiration, requiring periodic inhibition from a supramedullary "pneumotaxic center" to produce rhythmic breathing. The second theory, that of Hoff and Breckenridge,[19] views the medullary center as possessing intrinsic rhythmicity, with supramedullary and extramedullary impulses converging upon it to produce by summation the final respiratory act. If respiratory failure in bulbar poliomyelitis reflects progressive damage to the medullary respiratory center, the findings strongly support the view that rhythmicity is an inherent and extremely sensitive function of that center.

All available evidence indicates that central respiratory failure in poliomyelitis is medullary in origin. The medulla is the site of major pathological damage in patients suffering central failure.[4,20-22] Experimental physiological studies have demonstrated only in the medulla a dissociation in responsiveness to chemical and reflex stimuli, such as occurs in bulbar poliomyelitis.[23-25] Indeed, the pattern of development of respiratory failure in bulbar poliomyelitis bears a close resemblance to the manner in which respiration deteriorates in the medullary animal who has suffered anoxia, drug depression, or trauma.[26,27] Finally, unpublished observations on humans in our own laboratory indicate that supramedullary brain stem lesions affecting respiration produce sustained hyperventilation or Cheyne-Stokes respiration rather than the breath-to-breath variations in respiratory rhythm with hyposensitivity to carbon dioxide that is seen in centrogenic respiratory failure in poliomyelitis.

Little elaboration of the clinical implications of observations made during acute poliomyelitis is necessary. Evidence presented in the clinical descriptions indicates that the changes observed in these patients could not be attributed to respiratory obstruction: Pharyngeal secretions were carefully removed in all patients before recordings were made; some of the severest anomalies appeared in subjects who lacked swallowing paralysis, and establishment of tracheotomy with complete assurance of a clear airway failed to relieve the respiratory irregularity or to restore spontaneously adequate ventilation. Also, the respiratory defects could not have resulted from progressive involvement of spinal motoneurons serving diaphragm and intercostal muscles, since every patient demonstrated upon command the capacity for individual breaths which, if rhythmically sustained, would have been adequate to maintain respiratory compensation.

One clinical phenomenon which was searched for was never observed. This was incoordination of the respiratory muscles

themselves, resulting in expiratory and inspiratory groups contracting simultaneously. At times, retraction of the abdominal wall during inspiration gave the impression that active expiration was taking place, but fluoroscopic examination demonstrated diaphragmatic descent at this time and tidal volume showed no decrease. Wade[28] has emphasized how misleading abdominal movement may be in estimating the phase of diaphragmatic activity. He also reported inability to induce dissociation of inspiratory muscle groups. When respiratory rhythm was most markedly disturbed in poliomyelitis, the central respiratory discharge appeared to be either inspiratory or expiratory, and never a combination of the two. Incoordination of laryngeal activity with respiratory cycling was noted during both acute and convalescent poliomyelitis, but this could not be attributed to dysfunction of the respiratory center.

The defects in respiratory regulation persisting after poliomyelitis were unexpected. The view is widely held that, if the patient survives poliomyelitis, central regulation of respiration will return to normal.[29] The impairment of respiratory rhythm, hypoventilation during sleep, depression of ventilation by oxygen, and low CO_2 responsiveness, shown by F. L. and A. W., strongly suggest that these patients have abnormally functioning respiratory centers. Less clear is the cause of the persistent defects observed in the larger number of subjects in Groups B and C. These defects were largely confined to reduced respiratory sensitivity to carbon dioxide without evidence of impaired respiratory rhythmicity or significant suppression of breathing by oxygen. Similar findings in a series of convalescent poliomyelitis patients with markedly reduced breathing capacity recently were presented by Linderholm and Werneman.[30] These authors noted that low CO_2 responsiveness was selective and did not apply to their entire low-vital-capacity, low-maximal-breathing-capacity group. The ventilatory response to exercise appeared normal in their low-CO_2-responsive cases, and ventilation during work was greater than during CO_2 inhalation. The percentage of low-CO_2-responsive cases among their patients with pure spinal paralysis was as high as the percentage among patients having bulbar pareses. The highest incidence of low-CO_2-responsive cases, however, was among patients showing "cerebral" symptoms during acute poliomyelitis. Linderholm and Werneman concluded that low responsiveness to CO_2 after poliomyelitis was due to persistent damage to the medullary chemoreceptors. They attributed little clinical importance to the finding, save that it might create difficulties at times of future surgical intervention or anesthesia.

Permanent damage to chemoreceptive neurons in the respiratory center is an attractive explanation for the widespread finding of low CO_2 responsiveness after poliomyelitis. This explanation is supported by the observation that the indolent ventilatory responses to carbon dioxide were most prominent among patients who, clinically, had bulbar poliomyelitis. Permanent damage to central breathing mechanisms also would explain why impaired CO_2 sensitivity was not proportional to the reduction in the ventilatory ability when subjects within each group were compared. However, damage to the respiratory center is probably not the only cause of the impaired response to carbon dioxide during convalescence from poliomyelitis. Except in the case of H. W., low CO_2 responsiveness was never observed in convalescence among patients who had central respiratory failure unless they also suffered a significant restriction of MBC due to spinal paralysis. Isolated low responsiveness to CO_2 after poliomyelitis was nearly as frequent in patients who had had only spinal paralysis as it was in patients who also had suffered bulbar paralysis. The only common denominator to all patients who had a pronounced impairment in the ventilatory response to CO_2 was a restriction in the MBC or VC of 50% or more. At least part of the impaired sensitivity, therefore, may have been peripheral rather than

central in origin. Peripheral mechanisms recently have been concluded to have such an effect in pulmonary emphysema. Cherniak and Snidal [31] demonstrated that low CO_2 response curves in emphysema are directly related to the reduction in the level of the MBC. If the MBC of emphysema patients was increased, so was the CO_2 responsiveness, in a manner similar to that if the MBC of a normal subject is reduced by artificial airway obstruction, CO_2 re- noted in the case of R. W., reported here. Furthermore, Cherniak demonstrated that sponsiveness shows a proportionate decline.

Restriction of MBC and VC in poliomyelitis is associated with a pronounced loss of chest-lung compliance.[32] Reduced compliance, of necessity, imposes an increase above the normal in the work of breathing. Recent evidence [33] indicates that in emphysematous patients with restricted ventilation the increment in the work of breathing following CO_2 stimulation may be normal, although impaired pulmonary mechanics limits the ventilatory response. Thus, impaired CO_2 responsiveness following poliomyelitis in many instances may reflect merely an increase in the work requirements of breathing, and not any defect in the respiratory center.

Whatever its cause, reduced CO_2 responsiveness following poliomyelitis has important clinical implications. Emancipation from respiratory aid is an important goal during convalescence from poliomyelitis. The final, and usually the most difficult, step in the program of withdrawing respiratory aid is in enabling patients to sleep without artificial respiration. Extramedullary respiratory stimuli may be required to maintain respiratory homeostasis in the presence of low CO_2 responsiveness after poliomyelitis. Sleep eliminates many of these stimuli, producing the setting for respiratory decompensation to ensue. This was observed in F. L. whenever artificial respiration was withdrawn at night. A. W. and R. W. developed the same problem during respiratory infections. These findings indicate that there is a physiological basis for the claims of those convalescent poliomyelitis patients who state that they need artificial respiration in order to sleep, although they have what appears to be relatively good return of respiratory function. The findings also demonstrate that respiratory infections may induce insidious respiratory decompensation long after patients recovering from poliomyelitis have recovered apparently adequate ventilatory reserves.

Summary and Conclusions

Clinical, physiological, and pathological observations on the nature of central respiratory failure in anterior poliomyelitis are presented. Central respiratory disturbances were noted in 20 patients during acute illness and in at least 2 patients during late convalescence.

Central respiratory failure in acute poliomyelitis evolves through three stages. Respiratory rhythmicity is first impaired during sleep. Dysrhythmic breathing then persists into wakefulness, and conscious drives must be recruited to maintain respiratory regularity and compensation. Impaired chemosensitivity to carbon dioxide is indicated by depression of ventilation while the patient is breathing oxygen. Finally, the respiratory response to chemical, as well as to reflex and other neural, stimuli shows progressive impairment, and artificial respiration is required to maintain respiratory homeostasis.

Depressant drugs accelerate markedly the deterioration of central respiratory control in acute poliomyelitis.

Pathological studies were performed on two patients. Both showed marked inflammatory changes and small areas of necrosis in the ventrolateral reticular formation of the medulla.

Irregular respiration during sleep persisted in two subjects for many months after acute poliomyelitis. These same patients also demonstrated carbon dioxide retention without dyspnea, an impaired ventilatory

response to increased tensions of inspired carbon dioxide, and reduction in ventilation while breathing 100% oxygen. These physiological abnormalities were attributed to permanent abnormalities in the functioning of the medullary respiratory center.

Seven out of nine convalescent subjects with spinal poliomyelitis having MBC or VC values of less than 50% of the predicted normal also demonstrated subnormal responsiveness to carbon dioxide as a respiratory stimulus. It appears that in poliomyelitis, as in pulmonary emphysema, peripheral mechanisms restricting chest motion may contribute to an impaired ventilatory response to carbon dioxide.

The clinical and physiological findings in central respiratory failure in poliomyelitis support the theory that an intrinsic and sensitive function of the medullary respiratory center is to establish the rhythmicity of breathing.

Elizabeth McGowan and Charles A. Donaldson gave technical assistance. Dr. James W. Stephens, of the University of Colorado Medical Center, placed the clinical observations and pathological material from his case at our disposal. Dr. Raymond F. Hain, Director of the Laboratory of Neuropathology, assisted in the preparation and interpretation of the pathological material.

University of Washington School of Medicine (5).

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Neurological Syndromes Associated with Congenital Absence of the Odontoid Process

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Introduction

Although there has been a considerable interest recently in neurological syndromes associated with congenital malformations of the cervical spine and basiocciput,[1,2] absence of the odontoid process has not been emphasized. We have been able to find only 13 reports of this condition, describing a total of 15 patients.[3-15] Two cases occasionally included in discussions of this syndrome have been omitted from this report because a significant portion of the odontoid process was present (Cases 4 and 16[8]).

This condition is more than a medical curiosity, since six patients have had transient neurological symptoms[5,7,8,11-13] and permanent signs of cord damage have occurred in three.[8,9,15] Because previous reports have been concerned with the radiologic and orthopedic aspects, the following two cases are reported to show that this skeletal anomaly should be considered in the differential diagnosis of cervical myelopathy.

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Dr. E. H. Wood, Dr. J. Taveras, and Dr. P. Morales granted us permission to include Case 1.

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Report of Cases

CASE 1.—A 59-year-old man was admitted to the Neurological Institute in 1952. In 1946 he began to have progressive weakness of both legs, necessitating cessation of work in 1949. In that year, while parking an automobile, he suddenly stared ahead, took his hands from the steering wheel, and the car shot forward into a concrete garage wall. There was no definite injury or loss of consciousness, but he subsequently seemed to have more weakness on the right side, whereas it had been more marked on the left previously. In 1950 his gait disturbance became worse and he had to use canes to get about. He began to have weakness of the arms and became incontinent of urine. He was admitted to another hospital,

Fig. 1 (Case 1).—Frontal-plane tomogram of upper cervical spine demonstrating absence or hypoplasia of the odontoid process.

Fig. 2 (Case 1).—Pneumoencephalogram in frontal projection showing a moderate degree of dilatation of the lateral ventricles with cavum septi pellucidi.

where cervical myelography was normal. In the following year he became unable to walk.

He was slow to follow instructions and had difficulty in calculating, but there were no specific mental abnormalities or aphasic defects. There was no gross abnormality of the cervical spine. The cranial nerves were all normal. A marked spastic quadriparesis was present, more pronounced on the right. Deep reflexes were bilaterally hyperactive, and there were bilateral Babinski and Hoffmann signs. Position and vibratory sensation was markedly impaired in the arms and legs. Touch sensation was intact, but perception of pain was impaired below the fourth cervical dermatome.

The hemogram, serological test for syphilis, urinalysis, blood sugar and nonprotein nitrogen, and serum albumin and globulin were normal. Manometrics, cell count, and serology of the spinal fluid were normal, but the protein was 63 mg. per 100 cc.; the γ-globulin was 51%, and the colloidal gold curve was 555443300. Roentgenograms of the chest and skull were normal. Frontal-plane tomograms of the upper cervical spine showed absence or hypoplasia of the odontoid process (Fig. 1). A pneumoencephalogram demonstrated diffuse cerebral atrophy of moderate degree and communicating cysts of the cavum septi pellucidi and ventriculus Vergae (Figs. 2 and 3). On the air study, intermittent cord compression associated with subluxation of the atlantoaxial joint was clearly demonstrated (Figs. 4 and 5). Psychometric examination indicated borderline intellectual functioning and was interpreted as showing deterioration from an average or higher intelligence due to cerebral disease.

Fusion of the cervical spine was considered but was not carried out because of the patient's age, general condition, and relative immobility. He was provided with a collar to prevent excessive flexion of the cervical spine.

Case 2.—A 55-year-old mechanic was admitted to Montefiore Hospital on April 21, 1955. Three years previously he slipped and fell on a concrete pavement, striking his occiput. He did not lose consciousness; there was only slight occipital pain, and he returned to work immediately. Since that time he had been aware of a "pressure" sensation over the occiput and posterior cervical region, extending into the interscapular area but not into the arms; there was no true pain. Some time afterward he noted difficulty in walking and stiffness of the legs, which were only minimally progressive. There was no impairment in the use of his arms or hands in his work and no sphincteric disturbance.

General physical examination showed no abnormality. There was neither limitation of move-

Fig. 3 (Case 1).—Lateral projection of pneumoencephalogram showing ventriculus Vergae.

Fig. 4 (Case 1).—Lateral projection of pneumoencephalogram. The gas column in the upper cervical spine terminates abruptly at the level of the upper margin of the neural arch of the axis.

Fig. 5 (Case 1).—Lateral projection of pneumoencephalogram. Atlantoaxial subluxation is present with posterior tilt of body of axis.

ment nor excessive mobility of the cervical spine. His mental status was normal, and the cranial nerves were normal; there was no nystagmus, Horner syndrome, or impairment of trigeminal sensory functions. His gait was "spastic," with dragging and circumduction of both legs on a broad base. There was no detectable weakness anywhere, but tone was increased in all extremities, much less in the arms than in the legs. The deep reflexes were symmetrically hyperactive in all extremities, but the jaw jerk was sluggish. There were bilateral Hoffmann and Babinski signs, and bilateral ankle clonus was obtained. Cremasteric and abdominal reflexes were absent. There were no sensory abnormalities.

Normal laboratory data included complete blood count; serological test for syphilis; urinalysis findings; blood urea nitrogen; blood sugar, and pressure, cell count, protein, γ-globulin, serology, and colloidal gold curve of the spinal fluid. Roentgenograms of the cervical spine demonstrated absence of the odontoid process with no dislocation, as seen on the plain films and tomograms (Figs. 6 and 7). Myelography showed no obstruction.

Comment

Embryology.—The odontoid process develops from three ossification centers.[17]

Fig. 6 (Case 2).—Lateral roentgenogram of the cervical spine. The odontoid process is absent. There is no evidence of atlantoaxial subluxation.

Fig. 7 (Case 2).—Frontal-plane tomogram of upper cervical spine showing absence of the odontoid process. Opaque material is present within the skull as a result of a previous myelogram.

The two lateral centers appear in the fifth month, and the apical center is noted between the second and the fifth year. During the third or fourth year, the odontoid process unites with the body of the axis. The apical ossification center of the odontoid unites with the odontoid process proper in the 12th year. Congenital absence of the odontoid process results when the three ossification centers fail to develop.

*Clinical Features.**—It might be anticipated that lack of the odontoid process would create a dangerous instability of the atlantoaxial articulation. It is therefore noteworthy that the age of onset for neurological symptoms is quite variable, ranging from 8 to 56 years.

The clinical manifestations associated with this anomaly may be divided into four groups:

Group 1: In seven cases, severe cervical pain and marked torticollis followed immediately some kind of trauma to the neck.[3,4,6,8,14] Unusual mobility of the neck was noted only once,[10] and neurological abnormalities have not occurred in these patients.

Group 2: In five cases, trauma was followed by transient weakness of the extremities,[4,5,7,8,11] and dysesthesia occurred in two [7,11]; neck pain and torticollis occurred in only one of these patients, and only one was subsequently reported to have permanent neurological deficit.[8]

Group 3: Symptoms and signs of slowly progressive or permanent cervical myelopathy have occurred in five instances (Nievergelt,[8] Alajouanine et al.,[9] Schultz et al.[15]; present Cases 1 and 2). Torticollis and cervical pain have not been features of these cases. No trauma prior to the onset of symptoms was recalled in three. All five of these cases had evidence of corticospinal motor impairment below the neck; proprioception was involved in two and cutaneous sensation in only one.

Group 4: Two patients had solely cerebral symptoms, without evidence of cervical myelopathy or nerve root compression. Seizures and mental deterioration occurred in the case of Raskin,[13] and the patient described by Ford [12] had attacks of unconsciousness, vertigo, and visual disturbances. Case 1 of the present report also showed an intellectual deficit and had one ictal episode of uncertain nature, in association with signs of cervical myelopathy.

Roentgenographic Features.—Absence of the odontoid process may be demonstrated roentgenographically by anteroposterior, lateral, and "open-mouth" projections of the cervical spine. Films taken in flexion and extension aid in the evaluation of atlantoaxial dislocation, which has been demonstrated in at least 11 of these cases. Anteroposterior and lateral tomograms are important for precise delineation of the deformity. Myelography, using either air or an opaque medium, may demonstrate angulation or compression of the cord (Case 1, Fig. 4).

* Based upon analysis of 17 cases, including the 2 reported in this paper.

Pathology and Pathogenesis of Neurological Syndromes.—Because of the frequent history of trauma and the actual demonstration of atlantoaxial dislocation in most of these cases, it is probable that either direct compression of the cervical spinal cord or embarrassment of its vascular supply plays a role in the causation of neurological symptoms. The same mechanism has been implicated in those cases of delayed myelopathy reported to occur in patients with post-traumatic fracture and separation of the odontoid process.[15,19]

Postmortem examination has been performed in only two cases. In one, compression of the spinal cord was demonstrated.[6] In the other, Raskin found platybasia and a congenital malformation of the cerebrum.[13] In one other patient[15] laminectomy disclosed "adhesive arachnoiditis," but the nature of the pathological process in the underlying cord is not known. Nor is the exact nature of the myelopathy known in any of the other cases, including the two presently reported, since they have not been examined anatomically. The possibility, therefore, exists that in some cases absence of the odontoid process is a coincidental finding of no pathogenic significance, and that some other neurological disorder is present.

The cerebral symptoms in the case described by Ford were attributed to compression of the vertebral arteries,[12] while the seizures in Raskin's case were associated with a cerebral anomaly.[13] In Case 1 of the present report, the pathogenesis of cerebral symptoms is not known.

It has been suggested that post-traumatic resorption of the odontoid process may be responsible for absence of this structure.[9] The immediate appearance of symptoms after trauma in some cases and the lack of any history of trauma in others make it more likely that the condition is due to a failure of development.

Treatment

If the symptoms associated with congenital absence of the odontoid process are due to atlantoaxial dislocation, it would be reasonable prophylaxis to fuse this joint surgically. For one reason or another, however, this has been done in only three of the reported cases.[4,6,12] Two patients[9,15] are reported to have improved after decompressive laminectomy. In some of the cases with torticollis cervical traction has been of value.

Summary

Two cases are presented to show that cervical myelopathy may be associated with absence of the odontoid process. It is presumed that the excessive mobility of the atlantoaxial joint afforded by this anomaly causes trauma to the spinal cord directly or to its blood vessels and meninges.

Addendum

An additional case is summarized.

The patient is a 61-year-old white man who was admitted to the hospital with a four-year history of progressive weakness of the upper and lower extremities. There was no previous history of trauma. Roentgenographic examination of the cervical spine showed a hypoplastic odontoid process with the question of a remnant of the odontoid process attached to the skull. There was marked misalignment at the level of C1-C2.

A cervical myelogram made at another institution and reviewed in this hospital showed posterior displacement and compression of the spinal cord at C1. Although a recommendation for a spinal fusion was made, the patient has not, as yet, agreed to the surgical procedure.

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Neurochemistry and Therapeutic Endeavor

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Application of chemistry to problems concerning the nervous system has now been in progress for over two centuries. This account brings together, briefly, three very different types of study which have contributed to this application.

Chemical Composition

The first chemical studies of the nervous system were of its composition and had no very immediate application in therapy. Through the investigations of Hensing, John, Gmelin, and Lassaigne can be traced the gradual growth of knowledge of, first, the inorganic and then the organic constituents of nerve tissues during the 18th and the early 19th century. Vauquelin,[1] working about 1810, is noteworthy for his thorough attempt to account quantitatively for cerebral constituents by separating them into fractions in a way which retained all his material, so that he could present a balance sheet adding to 100%; he made systematic use of an organic solvent (ethanol) and a heavy metal precipitant (lead salts) to do so. These became standard reagents for such separations. The preponderance of French neurochemical workers at this time is notable and is in keeping with their dominance in chemistry as a whole, which had been associated with Lavoisier and attracted the young Liebig, from Germany, to study in Paris before he established himself in Giessen.

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As the main concern of the present lecture is with therapy, I shall consider in more detail another French worker, Couerbe, who made one of the first clear attempts at therapeutic application of this type of knowledge. Like Vauquelin and several workers before and after him, Couerbe's main technique consisted of the separation and analysis of cerebral lipids. However, he applied this method not only to the brain of animals but also to the human brain obtained post mortem from persons of different mental status.[2] Here he made a claim which contributed to his later discredit, for he stated that, whereas the phosphorus content of the brain of normal persons was 2% to 2.5%, in the brain of idiots he found 1% to 1.5% and in brains of the insane, 3% to 4.5%. He concluded that phosphorus was the exciting principle of the nervous system and desired to apply this knowledge in medicine.

This theme had an unfortunate sequel, for it contributed to a false impression that foods of high phosphorus content were valuable for intellectual activity: an idea popularized in the slogan *ohne Phosphor keine Gedank*, which Liebig[3] in 1851 discredited and mocked, but which survived this and other condemnations, and indeed appears to survive today in the successors to patent medicines.

The next major attempt to apply chemical knowledge of the brain to medical problems was that of J. L. W. Thudichum between 1865 and 1882. Thudichum's work with cerebral tissues began with a limited practical problem: to understand those changes in infections and fevers in which the brain appeared to be involved, especially the delirium of typhus. We shall meet again later this concern of 19th cen-

tury neurochemists with infectious diseases, which were, of course, among the major unsolved medical problems of the day, and which had prominent mental symptoms. Thudichum wrote [4]:

> To understand zymoses, to be able to counteract them by rational, as distinguished from empirical or accidentally discovered means, is only possible by the aid of a complete knowledge of the chemical constitution of all the tissues, organs and juices of the body, and of all their possible decomposition products. It is to reach this goal of complete knowledge that the medical chemist must spare no efforts, and it is to the increase of this knowledge that my best efforts during many years have been directed.

This goal, with respect to the brain, Thudichum pursued by means not very different from those of Couerbe: by detailed chemical analysis, fractionation, isolation, and characterization of compounds. He differed mainly in the thoroughness and extent of his work, with compounds very difficult to purify. To knowledge of cerebral lipids he made notable contributions, but it is significant that he almost ignored many types of compounds which would now be regarded as of more functional importance. He threw away the proteins and intermediary metabolites, with which so much present work is concerned, and envisaged a direct application in pathology of chemical findings; but he was not at all clear as to how that might come about.

> When the normal composition of the brain shall be known to the uttermost item, then pathology can begin its search for abnormal compounds or derangements of quantities. . . . I believe that the great diseases of the brain and spine, such as general paralysis, acute and chronic mania, melancholy, and others, will all be shown to be connected with specific chemical changes in neuroplasm. Here is a field for enquiry of the possession of which the guardians of refuges for the insane will hereafter, I have no doubt, endeavour to make good use. The knowledge of the composition and properties of neuroplasm and of its constituents will also aid us in devising modes of radical treatment in cases in which at present only tentative symptomatic measures are taken. In short it is probable that by the aid of chemistry many derangements of the brain and mind, which are at present obscure, will become accurately definable and amenable to exact treatment, and what is now an object of anxious empiricism will become one for the proud exercise of exact science.[4]

We can appreciate that, ultimately, it is possible that a fairly complete knowledge of the chemical composition of organs in health and disease will give rational basis for therapy. A few examples exist of limited application of this principle. But, in practice, investigators did not await the gathering of such knowledge. During Thudichum's lifetime they went ahead with a radically different type of study, which only now is being integrated with other aspects of neurochemistry.

Chemotherapy

The methods which I speak of were those of medicinal chemistry as it began in the last century. Whereas Thudichum had little to offer in therapy but hypotheses, the real power of organic chemistry in its application to medicine was already being displayed in the spectacular way in which relatively simple organic substances modified the activity of the brain. The first example of this appeared at the time so novel that it awaited 50 years for its application. I am referring here to surgical anesthesia, with synthetic chemicals, recognized as feasible about 1800 but not applied until the 1840's. It is remarkable how promptly a variety of organic substances were then examined as anesthetics.[5] Only one to two years after Long and Morton had played the leading part in showing surgical anesthesia to be feasible with ether, Simpson had examined a variety of other volatile organic compounds, and from them made his famous selection of chloroform. A few years later, Snow had examined an even wider range of compounds, and contributed amylene as the most valuable addition to ether and chloroform. He quotes experiments with animals and clinical trials in establishing it as a practical surgical anesthetic. Snow, Flourens, and others conducted excellently planned investigations of the actions of the new compounds, including the specifying of effective and toxic

dose levels. The nomenclature of different degrees or levels of anesthesia was largely due to Snow's studies of the 1850's.

I wish at present to emphasize that this constituted a new and successful way of applying chemistry to the nervous system. It had, in fact, two novel aspects, which I shall call the chemical and the therapeutic. 1. Regarding chemical aspects, it is to be noted that many of the compounds tested by Simpson, Nunnerly, and Snow were prepared specifically as potential anesthetics. Organic chemistry was then itself only rudimentary. The great proliferation of work with aromatic and heterocyclic compounds had yet to come; simple aliphatic compounds, such as found application in anesthesia, represented the growing point of the subject, featuring, for example, in the theory of types and in radical theories. 2. Secondly, the therapeutic novelty lay in a desire to make use of new properties found in synthetic organic chemicals. Though it may seem obvious, this outlook is to be contrasted with other attitudes, exemplified by those of Humphry Davy or of Thudichum. Davy observed and wrote clearly about the potentialities of surgical anesthesia with synthetic nitrous oxide in 1800, but he abandoned these studies as unscientific a short time afterward and turned to the more satisfying study of chemistry itself (see, for example, Duncum [6]).

By contrast, the work which actually yielded surgical anesthesia seems rash and unprincipled. For, by contrast to earlier pharmacological aids to surgery, the new chemicals produced a relaxed, unconscious condition. The therapeutic discovery consisted of realizing that such a condition produced by the new chemicals was eminently suitable for surgery. Subsequently, unconsciousness and relaxation became properties demanded in surgical anesthesia. The type of compounds used as volatile anesthetics has not greatly changed in the 100 years since their introduction. Thus, the beginning of chemotherapy, which I have just described, was also a very successful example of a new type of neurochemistry, which began by showing that the new anesthetics worked.

After the success of surgical anesthesia, there came a greater readiness to seek medicinal virtues among the new synthetic organic chemicals. The next successes again came in connection with the nervous system. I refer to the development between 1860 and 1900 of hypnotic and sedative drugs. Here, again, we can detect chemical and therapeutic invention, and also a third category, which I shall follow Paul Ehrlich in calling chemotherapeutic.[5]

1. The chemical part lay in the choice and synthesis of substances related to those already known to have some degree of hypnotic effect. Some hypnotic, as well as other, actions were recognized in ethanol, and this was made the occasion by B. W. Richardson for the examination of a series of alcohols, in the hope of finding compounds which retained the hypnotic properties of ethanol but were without its intoxicating action. A different type of logic led to chloral: In vitro this compound can easily yield chloroform, and it was hoped by Liebreich [5] that it would gradually break down in vivo to maintain a low level of chloroform sufficient for only light depression. Urethan was also designed as a therapeutic agent on the basis of anticipated physiological properties, and can be regarded as the precursor of the ureides, and ultimately of the barbiturates.

2. The therapeutic aspect of the production of hypnotics again lay in accepting the properties of the new drugs and adopting appropriate means of taking advantage of these. Although we now have a clear picture of sedation and hypnosis and of the situations in which compounds, such as chloral and the barbiturates, are effective, these actions were in practice discovered in the period now under discussion, and were not by any means self-evident. How limited is the type of sedation produced by barbiturates is made clear by the re-

cently discovered chlorpromazine and reserpine. Moreover, the conditions in which the early sedatives were initially tested, and indeed recommended, exemplified properties which investigators would have liked to have found in them. They included sleep or rest in persons disturbed by pain, fever, manic conditions, and epilepsy. In most of these conditions, the hypnotics were of little use. Where they were of value, therefore, we can regard the result as a therapeutic discovery, often made as a result of much observation and trial.

3. Finally, the chemotherapeutic method itself was largely developed in the production of hypnotics, together with antipyretics and local anesthetics in the 1880's and 1890's. This is not the general impression of chemotherapeutic development, but I must emphasize[5] that Ehrlich reintroduced the term chemotherapy before he commenced the investigations for which he is most famous and with which the name of chemotherapy is usually associated. In 1898, a decade before the discovery of Salvarsan (arsphenamine), Ehrlich wrote of "the synthetic construction of new therapeutic agents on the one hand, and the discovery of specific therapeutic products in living cells on the other" and called these two different methods the "chemotherapeutic and the bio-therapeutic."[5] Chemotherapy Ehrlich exemplified in terms of the hypnotics, the local anesthetics, and the antipyretics. He had himself taken part in the synthesis of local anesthetics and wrote of them in 1898 as follows:

> In cocaine, for example, the ester-like benzoyl radical (COC_6H_5) undoubtedly represents the anesthesiophore group, the tertiary amine contained in the basic portion representing an analogue of the auxochrome group and hence called the auxotox. This is bourne out by the fact determined by me that cocaine loses its anesthetizing properties when through methylation it is converted to a quaternary ammonium base.[6]

Those familiar with Ehrlich's work will recognize here his writing and terminology. When they were later applied to the antimicrobal agents with which Ehrlich's name is rightly associated, they did much to give the appearance of a new beginning, and antimicrobal agents tended to preempt not only the terms parasitotropic, auxotox, and toxophore but also the name of chemotherapy and a claim to the development of ideas on the synthesis of drugs, in which they played a smaller and less productive part than they are usually credited with. To Ehrlich and his contemporaries the production of arsenicals and dyestuffs was very much part of the same story as the formation of hypnotics and analgesics; Keane,[7] in 1910, wrote of all as "the new iatrochemistry."

The reason for describing this as part of neurochemistry is that practically all the essential features of the new iatrochemistry were established in producing agents which acted on the nervous system. At the end of the last century the most pressing problems in medicine were those of infectious diseases. These problems were the subject of continuous therapeutic trials, for the existence and effects of quinine had shown the feasibility of treatment by administered chemical substances. The pyrexia of many infectious diseases caused disturbances of the central nervous system which were prominent among the symptoms of infection. Indeed, Thudichum, as has already been noted, wrote of the relevance of his studies to cholera and typhoid in seeking their practical application. Thus it is understandable that the simple aromatic compounds were first administered with the intention of curing infectious disease. This possibility seemed excellently confirmed when substances such as salicylic acid and acetanilid were indeed found to reduce body temperature in typhoid and puerperal fever. Only later were they demonstrated to do so by action on the heat-regulating centers of the medulla, with comparatively little effect on the course of infection. In the meantime, however, these and related compounds had been found to have a different central effect, which soon became the main occa-

sion for their administration: They were mild analgesics. The same story is to be told of the first synthetic heterocyclic compounds which found application in medicine: the quinoline derivatives and the pyrazalones made initially in imitation of quinine. These substances (kairine, thalline, antipyrine, and congeners) were again found to lower body temperature in fevers, but by central action, with which, again, was associated analgesia.

These briefly summarized investigations can be regarded as an experiment lasting a century, in which representatives of all the main classes of newly produced organic compounds were administered to animals or to men and their effect on the whole body explored. They produced actions other than those noted: Aromatic amines showed then, as now, an unfortunate tendency to cause methemoglobinemia. But of the properties which could be applied in medicine, it is to be noted that almost all refer to action at the brain: surgical anesthesia, hypnosis or sedation, antipyresis, and analgesia. The central nervous system proved the major target for the new medicinal chemicals. This has its parallel in other aspects of the chemical susceptibilities of the brain, for the brain is also the most sensitive part of the animal body to change in the level of many normal bodily metabolites, a peculiarity described in attractive detail by Barcroft.[8]

In the present century, as in the past, chemotherapy has proved the most successful of the applied branches of neurochemistry. Production of for example, anticonvulsants and morphine-like analgesics, and, more recently, of specific excitants and depressants of the central nervous system for use in mental illness are well known and have employed the combination of chemical synthesis, biological assay, and clinical trial developed in discovering the compounds already described.

Metabolic Contributions

The aspects of neurochemistry at present most intensively studied are metabolic. These also have given notable therapeutic contributions: the success of thiamine, pyridoxine, and nicotinamide is part of general medicine. An important link is now appearing between metabolic and nutritional disorders, in the conditions in which metabolic peculiarities make persons abnormally exacting nutritionally. Thus, children have been encountered who on normal diets suffered intractable convulsions, which were cured by unusually high doses of pyridoxine.[9] A further example is given by a familial amino-aciduria in which loss of tryptophan has serious consequences.[10,11] In some subjects so affected, the predominant symptoms are those of pellagra, and the associated mental disturbance has resulted in the subjects appearing in mental hospitals.[12] In instances investigated at the Maudsley Hospital an abnormality of indole metabolism was discovered which was seen most simply as an indicanuria.[10] The pellagra could then be recognized as due to a diversion of tryptophan metabolism, involving the production of indican, for in normal subjects probably more than half the daily requirement for nicotinamide is met by synthesis from tryptophan.

Metabolic studies of the brain in situ and of isolated cerebral tissues have been in the main interpretative. They have, for example, given basis for the action of many drugs and nutritional factors. A recently developed means of displaying such actions employs isolated, electrically stimulated cerebral tissues.[13] This has proved the most sensitive in vitro system to the action of several substances, including chlorpromazine,[14] which has a major blocking effect at 5μM., a level corresponding to that found after its administration at therapeutic dose levels. In vivo, quantitative measurement of cerebral metabolism[15] has been important in turning chemical research in schizophrenia away from rather barren speculation regarding abnormality in cere-

bral respiration, by showing the over-all respiratory rate in such conditions to be normal. However, exchange between the blood stream and the brain is proving more varied than had previously been supposed. A new category of substrate has now been found to undergo reaction there, and to contribute to an apparent arteriovenous difference in glutathione.

Thus investigators in the newly proliferated subject of neurochemistry are presented with an intriguing combination of very effective drugs of largely unknown action, of metabolic and chemical knowledge awaiting application, and of unsolved problems of major practical and social importance. It appears certain that chemistry has much more to add to therapeutic endeavors in mental and emotional disorders, for the brain, like other parts of the body, consists of chemical compounds and has no means for its maintenance other than continuous material supplies.

Summary

Application of chemistry to problems concerning the nervous system is surveyed, including studies of the chemical composition and metabolism of the brain. It is pointed out that a major part of the development of chemotherapy during the last century took place in relation to the central nervous system.

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Interhemispheric Communication Through the Corpus Callosum

Mnemonic Carry-Over Between the Hemispheres

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The early brain anatomists assumed highly important functions for the corpus callosum in relating and coordinating the activities of the two cerebral hemispheres. Likewise, the early clinical neurologists believed that destruction of this largest of all fiber tracts in the brain would result in serious functional defects, even in a general intellectual deterioration. However, actual observations on the effect of complete surgical section or of total agenesis of the corpus callosum in man and other animals have indicated a surprising absence of deficit.[1-6,8,9] This wide discrepancy between the expected and the actual effects of callosal damage has remained one of the enigmas of brain function.

Recent investigations of contralateral transfer of training in callosum-intact and callosum-sectioned animals, however, begin to reveal a definite role for the corpus callosum in the realm of "psychic" function. In the cat with the crossed retinal fibers divided at the optic chiasm, visual discriminations learned with one eye are recalled readily with the other eye, whereas such recall fails entirely when callosum also was sectioned prior to training.[12,13,16] Similarly, in the normal cat, discriminative learning with one forepaw is distinctly aided by prior identical learning with the other forepaw, whereas this cross benefit fails in the callosum-sectioned cat.[17] Thus, in the cat, one hemisphere seems in some way to benefit from the prior training or experience of the other hemisphere through intercommunication via the corpus callosum.

The present paper is an attempt to investigate further the nature of the callosal contribution. Does one hemisphere establish lasting memories of its own training or experiences in the other hemisphere, or does it merely make available to the other hemisphere mnemonic-loaded information for its sampling or use, without permanent contralateral trace establishment?

The general plan involved the destruction of crossed retinal fibers at the optic chiasm and subsequent establishment of pattern discrimination learned through one eye. The visual cortex plus varying amounts of adjoining cortex were then removed from the hemisphere receiving impulses from the trained eye. Survival of the learned responses was thereafter tested through the untrained eye. Preservation of the learned discrimination under these conditions would indicate the establishment of a duplicate memory system in the contralateral hemisphere.

Methods

Animals.—Fourteen cats were used, all of them laboratory-reared from an age of 6 weeks or younger. At the start of the present experiment they ranged in age from 7 to 14 months and had had no prior experience with formal visual training.

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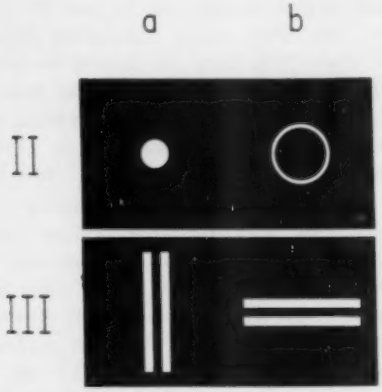

Fig. 1.—The two pairs of visual discrimination patterns. The left one of each pair was the positive (rewarded) pattern. The designations correspond to those in a preceding study.[39]

Surgical Procedures.—Section of the crossed optic fibers at the chiasm was effected through a transbuccal approach, as previously described.[38] The cortical ablations, carried out after establishment of the learned responses, were performed with routine neurosurgical techniques, the brain tissue being removed by suction. The extent of the cortical removals is described below.

Training and Testing Procedures.—The mask used during the periods of training and testing to occlude one or the other eye was constructed of soft black rubber sheeting and was held snugly in place by ties to a leather collar.

Two different discrimination problems were used. The paired test patterns for these are pictured in Figure 1. Discrimination on the basis of total luminous flux, rather than pattern, was ruled out in this study by designing the positive and negative patterns of equal area. Further, tests run with an imposed brightness difference between the patterns, with the more brightly transilluminated figure varying between the positive and the negative pattern, did not disrupt the response. The same training box and procedures were used as described earlier.[12] In establishing a discrimination, the two patterns of a pair were presented side by side, and the cats were trained to choose one of the two. The two patterns were switched from side to side according to a chance sequence to avoid development of side preference. After the cats attained correct performance of 34 or more trials out of 40, the responses were further stabilized by 400 overtraining trials, run in sessions of 40 per day.

Postoperative tests with the mask covering the trained eye were started on the 12th day following the cortical ablation, and, where immediate recall was not apparent, were continued in most cases until high-level performances were obtained.

Anatomical Controls.—When the behavioral testings were completed, the cats were given a lethal dose of pentobarbital and perfused with 10% formalin. The brains were removed, and completeness of chiasm section was confirmed by gross dissection and removal of the tantalum foil insert (Myers[12]). Determinations of extent of the cortical removals based on careful study of the gross brain specimens and gross brain sections proved adequate for the purposes of the experiment.

Three types of cortical removals were performed, as illustrated in Figure 2. The *minimal*-type lesion, as seen in Case *Msy*, was restricted to removal of an area approximately coextensive with the primary visual area as mapped by Talbot and Marshall.[38] The *moderate*-type lesion involved removal of this area plus adjoining, physiologically related cortex, as shown in *Chr*. Both types of lesions extended medially and ventrally to include the superior bank of the sulcus splenialis, leaving gyrus splenialis intact. The *maximal*-type lesion

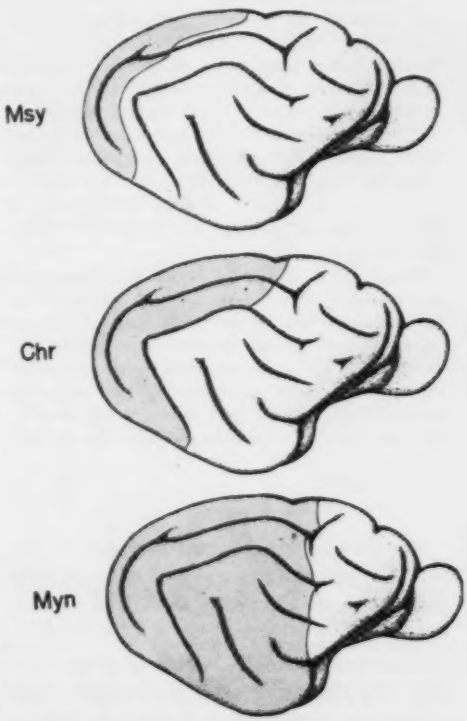

Fig. 2.—Stylized diagrams illustrating extent of cortical removal in the three lesion types. Variations in extent of lesion within a group were minor.

TABLE 1.—*Performance with Untrained Eye on Discrimination III After Destruction of Contralateral "Trained" Cortex*

Cat	Eye Tested	Lesion Type	Test Performance on Successive Days as Number Correct in Sets of 40		
			1st	2d	3d
Msy	L	R; minimal	37	--	--
Msf	L	R; minimal	37	--	--
Grs	L	R; minimal	20	36	40
Fst	R	L; moderate	30	38	38
Pln	R	L; moderate	27	40	--
Crw	R	L; moderate	28	32	38
Spe	L	R; moderate	33	38	--
Csw	L	R; moderate	40	--	--
Sch	L	R; moderate	37	--	--
Chr	L	R; moderate	30	--	--
Nkm	R	L; extensive	7/10 *	--	--
Kmn	R	L; extensive	37	--	--
Myn	L	R; extensive	27	37	40

* Nkm refused to run after 10 test trials, having erred in the last 3.

represented removal of all neocortex posteriorly with complete preservation of cortex anterior to and including the posterior sigmoid and coronal gyri (Case *Myn*). Variations in the extent of removal within these three groups were so slight as not to merit separate consideration. Removals in all cases extended through the entire depth of the gray matter and into the immediately subjacent white matter. The deep-lying ganglionic masses, including amygdala, were not encroached upon by the lesion and, as may be seen from Figure 1, *Myn*, the piriform cortex was preserved without damage.

Behaviorally, no bizarre effects were noted and no apparent alteration found in emotional behavior. There was demonstrable, however, the expected loss of visual responsiveness in the eye ipsilateral to the lesion, as tested by confrontation. In the cats with extensive lesions, transitory postural abnormalities were noted in the extremities contralateral to the lesion, which cleared within 5-10 days.

Results

The results obtained in the use of the two discriminations are described separately and are separately summarized in Tables 1 and 2.

Discrimination III.—Minimal-Type Lesion: Of three cats with the minimal-type lesion, two performed well from the beginning of testing with the untrained eye on Discrimination III. Each of these two cats made only 3 mistakes on the first 40 trials, and these were widely distributed through the trials. The third cat showed an apparently chance performance on the first set of 40 runs but achieved a high-level performance on the second and a perfect performance on the third set of 40 trials.

Moderate-Type Lesion: Among the seven cats with the moderate-type lesion three showed high-level performance on the first set of 40 trials; three, high-level performance on the second set of 40 trials, and the remaining cat, high-level performance only on the third set of 40 trials. In the case of all cats with the moderate-type lesion the performance level was well above chance on the first 40 trials.

Maximal-Type Lesion: Of the three cats with the maximal-type cortical removal, two showed good retention on the first trials, though one of the two, Nkw, a very anxious cat, refused to continue further trials after having run the first 7 of 10 correctly. The third cat, with extensive removal, after having shown significant retention on the first 40 trials, achieved high-level performance on his second 40 trials.

The two types of results obtained with the cats on Discrimination III are illustrated in Figure 3. The curves of *Chr* demonstrate the usual slow learning rate during initial training and the almost perfect recall on test trials with the untrained eye. The curves of *Myn* indicate only partial recall, with, however, clear-cut saving in relearning with the untrained eye.

Discrimination II.—Discrimination II is the more difficult discrimination of the two,

TABLE 2.—*Performance with Untrained Eye on Discrimination II After Destruction of Contralateral "Trained" Cortex*

Cat	Eye Tested	Lesion Type	Test Performance on Successive Days as Number Correct in Sets of 40			
			1st	2d	3d	4th
Chr	L	R; moderate	25	25	25	32
Myn	L	R; extensive	18	21	21	25
Bhf	L	R; extensive	23	--	--	--

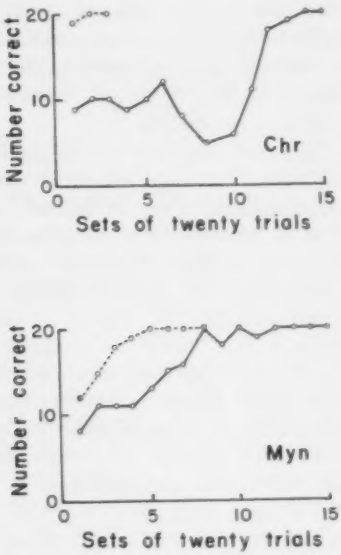

Fig. 3.—Performance of *Chr* and *Myn* on Discrimination III. The solid line represents initial training with one eye, while the dashed line indicates the performance on test trials using the second, untrained eye. *Chr* illustrates immediate recognition with the untrained eye, while *Myn* shows considerable saving in relearning with the untrained eye.

as gauged by the far greater number of trials required for initial learning and by the general behavioral response of the cats during training. Only three cats were tested on this discrimination—one having the moderate and two the extensive lesion. The cat with the moderate-type cortical lesion showed little, if any, immediate retention and only suggestive evidence of saving in relearning of this response with the untrained eye, as demonstrated best in the graph of Figure 4 (*Chr*). Cat *Myn*, with the extensive lesion, showed also no immediate retention and little indication of saving on relearning with the untrained eye (*Myn*, Fig. 4). Cat *Knt* was tested only for 40 trials and showed no apparent retention.

Comment

Destruction bilaterally of the primary visual cortical areas in the cat results in loss of pattern discriminations of the sort used in the present experiment. In like manner, transection of the great cortical commissure, the corpus callosum, completely prevents visual gnostic intercommunication between the brain halves in the cat (see Introduction). These facts point to cortex (and associated thalamic nuclei) as the probable site of elaboration of visual sensory input. The contribution of brainstem mechanisms to such high-level, "phychic" activity has yet to be fully explored. Present evidence, however, points toward involvement of brain stem in preparing and maintaining levels of activity in the cortex necessary for such high-level functions, rather than toward a primary involvement in these functions.[7,11] Accordingly, it is assumed in the following discussion that the memory mechanisms underlying the involved pattern discrimination responses re-

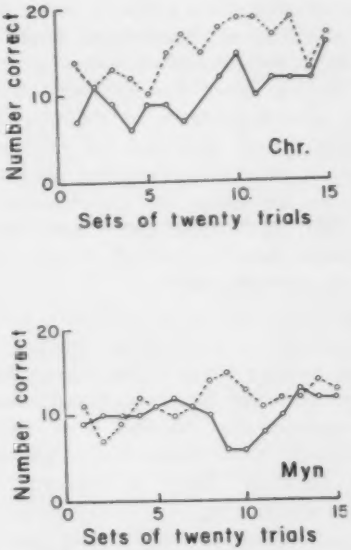

Fig. 4.—Performance of *Chr* and *Myn* with Discrimination II on initial training, using one eye (solid line), and on retraining, using the opposite, untrained eye (dashed line). Training and testing procedures with this response were not strictly comparable, owing to need for variable encouragement. Therefore only the first 300 trials with each eye are represented. Neither cat shows definite indication of immediate recognition with the untrained eye. On the contrary, only slight saving is suggested on retraining in the case of *Chr* and no saving in the case of *Myn*.

side somewhere within the cortical gray mantle, or at least can be grossly disorganized by appropriate cortical insult.

Widespread destruction of the cortex of the "trained" hemisphere does not destroy recall of the simpler Discrimination III by the opposite "untrained" hemisphere, though some uncertainty is seen on test performance in a few instances. On the other hand, there is complete or near-complete loss of memory for the more difficult Discrimination II, and it is necessary to reteach this response to the untrained eye. A closely similar outcome, with good preservation of the simpler and loss of the more difficult discrimination, has been seen on tests with the "untrained" hemisphere of chiasm-sectioned cats having transection of the corpus callosum subsequent to training but prior to testing.[15] However, section of the corpus callosum in this latter study did not noticeably affect levels of performance with the "trained" hemisphere, though this was often the hemisphere receiving retraction during entry for callosum section. Such close dependence of the results on training history and lack of relation to fortuitous surgical manipulation render unlikely the suggestion that gnostic losses of the "untrained" hemisphere are due to "threshold diaschisis" effects secondary to the surgical procedures.

One hemisphere seems, therefore, to have the capacity to establish well-marked and lasting memory traces in the opposite hemisphere through the corpus callosum if the communication handled is of simpler dimensions. With more difficult transmissions, however, there is apparent lack of contralateral engram establishment, with loss of recall capacity contralaterally on section of the corpus callosum or destruction of ipsilateral "trained" cortex. It must be noted at this time that cats with chiasm section alone, without the superimposed callosal or cortical lesions, have no difficulty in recalling the more difficult Discrimination II on transfer tests with the untrained eye. It may be inferred from this that the cortex removed from the "trained" hemisphere normally must contribute actively and substantially to performance with the "untrained" hemisphere at the time of responding.

Two activities may then be distinguished for the corpus callosum in visual gnostic intercommunication. The one, limited somewhat in its capacity, may result in establishment of a lasting contralateral memory trace somewhat less well developed than on the trained side. This activity is accomplished at a time prior to testing. The second activity, though not effective in further trace establishment, contributes potently to discriminative response and is achieved at the time of testing. The relationship between these two contributions is not known. It seems most likely that they are aspects of one and the same mechanism, which may affect neuronal events of the opposite hemisphere in lasting, as well as nonlasting, supportive ways. Fuller understanding of these results in terms of neuronal events, however, awaits further investigation.

No gross differences were seen among the cortical lesion types in their effects on performance level with the opposite, "untrained" neural apparatus, as seen from Tables 1 and 2. Differences in performances were far greater within than between lesion types, and greater deficits were not necessarily seen with greater lesions. This approximate equivalence of the lesion types would support the concept that neural tissue beyond the more restrictive removal contributes little toward the maintenance, and presumably also the development, of stable contralateral memory effects. The cortex in and around the visual receptive areas would then appear not only to receive the visual impulses from the retina but also to integrate and subsequently to intercommunicate between the hemispheres the significance of this experience. Data indicating a posterior localization of the visual gnostic transfer function of the corpus callosum tends to lend further support to this

interpretation, in view of the primarily homologous nature of the callosum interconnections.[14]

Summary

Fourteen chiasm-sectioned cats were taught visual pattern discriminations with one eye masked. Thereafter the primary visual area, plus varying amounts of adjoining cortex, was removed from the hemisphere of the trained side. Beginning 12 days after the cortical removal, the cats were tested for their ability to recall the response with the untrained eye. Recall was immediate, or nearly so, for the simpler discrimination. Recall failed, however, in the case of the more difficult discrimination. Amount of cortical tissue removed beyond the receptive area did not appear to affect this outcome.

The results demonstrate that the hemispheric intercommunication through the corpus callosum is sufficiently developed to establish independent memory traces in the opposite hemisphere when the involved integration is of simpler dimensions, but may fail when the problem is more complex. It is shown also how one hemisphere may actively contribute to the performance of the other at the time of response through the corpus callosum.

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Cerebrospinal Fluid Free Cholesterol as Index of Activity of Multiple Sclerosis and Allied Diseases

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With the Technical Assistance of Firmin Snodell, B.S.

One of the vexing problems in neurology is the lack of objective criteria for evaluating the degree of activity of the demyelinizing process in patients with multiple sclerosis and allied diseases. The very nature of these diseases makes it extremely difficult to translate signs and symptoms into terms of activity. An actively demyelinizing lesion may be hidden in a "silent" area of the nervous system, while symptoms which appear to indicate progression of the disease may actually be manifestations of the reparative process of gliosis. The various disability scales that have been proposed for measuring the severity of the disease fail to take into account the fact that old lesions, which are quiescent or healed, may prevent the appearance of new symptoms and signs indicative of renewed demyelinization. The evaluation of proposed therapeutic regimens has been hindered by the fact that prolonged periods of observation are necessary for appreciation of their effects, and, chiefly, by the lack of an objective laboratory method to measure activity of the disease process.

Esterification of free cholesterol in white matter is a characteristic of demyelinization.[1,2] This fact led us to investigate the possibility that changes in the composition of the cholesterol fractions in the cerebrospinal fluid (CSF) might reflect this biochemical alteration in multiple sclerosis and other demyelinizing diseases.

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Material

The patients used in this study were hospitalized at the University of Kansas Medical Center or the Kansas City Veterans' Administration Hospital. The patients were unselected and were personally examined by one of us (C. M. P.). The clinical diagnosis and evaluation of "activity" of the disease process was made before CSF-cholesterol determination. Cerebrospinal fluid was obtained during the course of routine diagnostic lumbar puncture. In a few instances fluid obtained at the time of pneumoencephalography was used. The fluid was thoroughly mixed and an aliquot taken for the study. On several occasions ventricular fluid was similarly used. Determinations of cell count, total protein, and colloidal gold curve were performed in each instance. The fluid was placed in sterile test tubes and stored at —20 C for varying periods of time before analysis.

Method

From 12 to 20 ml. of CSF is measured with a serological pipette and extracted with hot acetone-alcohol in a 100 ml. volumetric flask. The flask is allowed to cool to room temperature and is made to volume with acetone-alcohol. The contents of the flask are then filtered, and two 40 ml. aliquots are pipetted into 125 ml. Erlenmeyer flasks—one for total- and the other for free-cholesterol determination. The contents of each flask are then evaporated to dryness in a 75 C water bath under a constant stream of nitrogen. Care must be taken to see that the flasks do not remain in the water bath any longer than is necessary for complete evaporation.

The acetone-alcohol-soluble portion of the residue in each flask is then transferred to tubes in the following manner:

About 1 ml. of acetone-alcohol is pipetted into each flask and heated in a 60 C water bath for about one minute. With a bulb pipette the residue

in the flask is agitated, and the inner walls of the flask are washed several times with this portion of solvent, which is then filtered into the tube. This procedure is repeated two more times, giving a volume of about 3 ml. in each tube.

The quantity of digitonin-precipitable sterol in each tube is then determined by the turbidimetric method of Costello and Curran,[8] with the following variations:

1. In the determination of total cholesterol the contents of each tube are saponified with 2 drops of 50% potassium hydroxide solution instead of 1 ml. of the acetone-ethanol solution of potassium hydroxide.

2. Owing to the small quantities of sterols in most CSF specimens, the slight increase in optical density resulting from the digitonin solution itself must be taken into account. For this reason, a reagent blank should be run. This optical density (O. D.) is then subtracted from the O. D. of the unknown. We have found the O. D. due to reagents to be constant and to have a value of 2 units when the Klett-Summerson photoelectric colorimeter is used.

$$\frac{(0.2)(\text{O. D. of unknown}-\text{O. D. of reagent blank})(100)}{(\text{O. D. of standard})(0.4)(\text{ml. of CSF})} = \text{Mg. \% digitonin-precipitable sterols}$$

Whenever possible, duplicate determinations were performed, but in most cases the limited quantity of CSF permitted only single analysis. Parallel determinations of cholesterol in several instances by the method of Sperry and Webb[4] indicated that, as in serum, about 90% of the digitonin-precipitable sterol in CSF consists of cholesterol. The least amount of CSF sterol determinable under these conditions is 0.03 mg. %.

Results

1. *Normal Controls.*—Normal controls consisted of 25 patients with nonspecific headaches, idiopathic or post-traumatic epilepsy of long duration, or psychoneurosis. In all cases the neurologic examination and various laboratory tests, including CSF examination of cell count, total protein, serology, and colloidal gold curve were within normal limits. The age of the patients ranged from 11 to 62 years, with a mean age of 34 years. There were 14 male and 11 female subjects in this group. All these patients were considered to be free of any organic parenchymal disease of the nervous system.

Total protein in the CSF ranged from 31 to 47 mg. %, with a mean of 31 mg. %. Total CSF cholesterol ranged from 0 to 0.29 mg. %, with a mean of 0.11 mg. %. The CSF of none of the normal controls contained free cholesterol. Since the least amount of sterol determinable by the method used is 0.03 mg. %, it can be said only that under these procedural conditions, normal CSF contains no demonstrable content of free cholesterol.

TABLE 1.—*Cerebrospinal Fluid Cholesterol in Neoplasms and Infections*

	Normals	Neoplasms	Infections
No. of determinations	25	11	38
Mean CSF total cholesterol, %	0.11	1.4	0.84
Mean CSF free cholesterol, mg. %	0	0.43	0.41
Mean CSF total protein, mg. %	31	113	89

No correlation could be demonstrated between the level of serum cholesterol and the CSF cholesterol content. No statistically significant correlation exists between the CSF protein and the CSF cholesterol in these control fluids.

2. *Neoplasms and Infections of the Central Nervous System.*—Eleven patients with a variety of neoplasms of the central nervous system were included in this group (Table 1). The tumors were histologically identified and consisted of two glioblastomas, two astrocytomas, and a meningioma, neurofibroma of spinal root, acoustic neurinoma, medulloblastoma, colloid cyst of the third ventricle, metastatic carcinoma of undetermined origin, and chromophobe adenoma of the pituitary gland, one each.

The total protein ranged from 6 to 500 mg. %, with a mean of 113 mg. %. Total CSF cholesterol ranged from 0 to 5.6 mg. %, with a mean of 1.4 mg. %, while free CSF cholesterol ranged from 0 to 2.2 mg. %, with a mean of 0.43 mg. %.

Thirty-eight determinations of total- and free-cholesterol content were performed on CSF from 20 patients affected with bacterial, viral, and fungal diseases of the

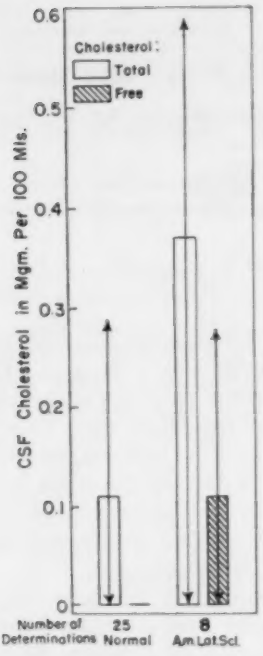

Fig. 1.—Cerebrospinal fluid cholesterol in amyotrophic lateral sclerosis. Bars represent the mean value; double arrows represent the range of values.

nervous system at different stages of their diseases. Total protein ranged from 18 to 500 mg. %, with a mean of 89 mg. %. Total CSF cholesterol ranged from 0.05 to 4.6 mg. %, with a mean of 0.84 mg. %, while free CSF cholesterol ranged from 0 to 2.6 mg. %, with a mean of 0.41 mg. %.

In neoplasms and infections of the nervous system a statistical correlation ($P<0.01$) could be established between the CSF total protein and both total and free CSF cholesterol.

3. *Amyotrophic Lateral Sclerosis* (Fig. 1).—Eight determinations were carried out on six patients with amyotrophic lateral sclerosis. The total CSF protein ranged from 39 to 68 mg. %, with a mean of 53 mg. %. Total CSF cholesterol ranged from 0.05 to 0.59 mg. %, with a mean of 0.37 mg. %, while free CSF cholesterol ranged from 0 to 0.28 mg. %, with a mean of 0.11 mg. %.

The mean total cholesterol, of 0.37 mg. %, differed significantly by statistical analysis from the mean normal CSF total cholesterol of 0.11 mg. %. The presence of free CSF cholesterol in amyotrophic lateral sclerosis is, of course, significant when compared with the absence of free cholesterol in the CSF of normal controls.

In one patient with amyotrophic lateral sclerosis, during a prolonged period of hospitalization the following observations were made (Fig. 2): At the time of the first lumbar puncture, in July, 1956, the patient had complained of weakness of the right hand for three weeks. Many neurologic signs were observed which were suggestive of amyotrophic lateral sclerosis involving the spinal and bulbar tracts, as well as the pyramidal tracts. For the next month the patient's signs and symptoms definitely progressed, but thereafter his clinical status remained unchanged. The CSF was examined again in December, 1956. At this time the patient's neurologic status was essentially unchanged from that in October,

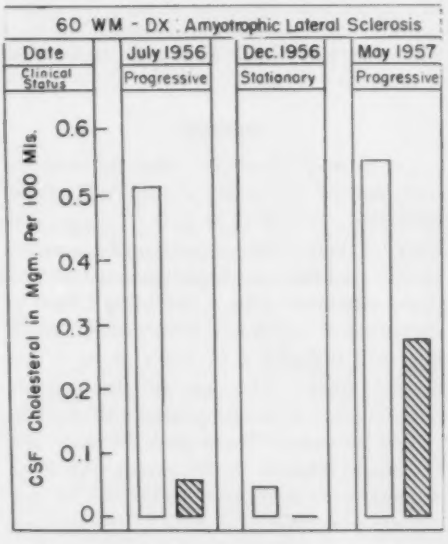

Fig. 2.—Serial determinations of CSF cholesterol in a patient with amyotrophic lateral sclerosis. Clear bars represent total CSF cholesterol; hatched bars, free CSF cholesterol.

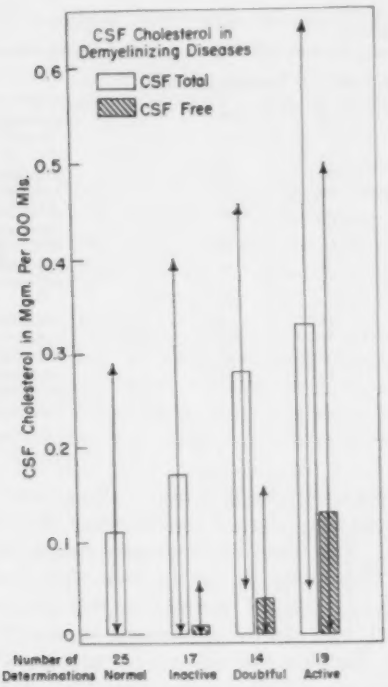

Fig. 3.—CSF cholesterol in patients with multiple sclerosis. Comparison of values for normal controls and inactive, questionably active, and active cases. Bars represent mean values; double arrows represent range of values.

1956. The total CSF cholesterol was within normal limits, and no free cholesterol was present. The patient again showed signs of progression of his disease in April, 1957, and the CSF obtained in May, 1957, revealed a sharp elevation of total CSF cholesterol (0.55 mg. %) with 0.28 mg. % of free cholesterol. In this patient a striking correlation could be established between clinical activity and the presence of free CSF cholesterol.

4. *Multiple Sclerosis and Other Demyelinizing Diseases* (Fig. 3).—Included in this group of patients with well-documented multiple sclerosis were several cases of so-called primary lateral sclerosis, acute transverse myelitis, acute retrobulbar neuritis, acute disseminated encephalomyelitis, and diffuse sclerosis of the Schilder type. Fifty determinations of CSF cholesterol were made on 39 patients. The patients were divided into three groups according to the examiner's evaluation of activity on purely clinical grounds, taking into account the approximate date of onset of most recent symptoms and progression or resolution of symptoms and signs. Thus, 17 cases were classified as inactive and 19 cases as defi-

TABLE 2.—*Cerebrospinal Fluid Cholesterol in Patients with Inactive Multiple Sclerosis*

Patient	Age	Sex	Date	Cerebrospinal Fluid *				
				WBC	TP	TC	FC	Colloid. Gold Curve
1	11	F		0	26	0.12	0	0000000000
2	29	M		2	40	0.11	0	0122110000
3	50	M		1	50	0.40	0.06	1112211000
4	29	M		10	74	0.22	0.06	5554321000
5 †	33	F	10/15/56	3	35	0.20	0	5543211000
6	47	F		0	35	0.21	0	0000110000
7	36	M		4	27	0.10	0	0000000000
8	25	F		2	39	0.12	0	0121100000
9 ‡	36	M	6/12/56	2	34	0.16	0	1122100000
9a ‡	36	M	6/26/56	2	37	0.26	0	1123210000
10	51	M		3	49	0.26	0	0011100000
11	53	F		7	39	0.12	0	5555443221
12	31	M		4	26	0	0	0000000000
13	36	M		8	40	0.33	0	0112211000
14	48	M		4	64	0.17	0	5522100000
15	9	F		0	13	0	0	0000000000
16	38	F		2	31	0.13	0	5543221000

* WBC, leukocytes per cubic millimeter CFS; TP, total protein, in milligrams per 100 ml. CSF; TC, total cholesterol, in milligrams per 100 ml. CSF; FC, free cholesterol in milligrams per 100 ml. CSF.

† See Patient 7, Table 4.

‡ See Patient 11, Table 4.

TABLE 3.—*Cerebrospinal Fluid Cholesterol in Patients with Questionably Active Multiple Sclerosis*

Patient	Age	Sex	Date	Cerebrospinal Fluid				
				WBC	TP	TC	FC	Colloid. Gold Curve
1	39	M		1	48	0.43	0.09	0001110000
2	38	M	5/22/56	29	50	0.22	0	5553211000
2a	38	M	6/12/56	10	42	0.32	0	0112211000
2b	38	M	6/25/56	3	46	0.31	0	0122321100
3	31	F		5	37	0.46	0.06	0122210000
4	45	M		1	45	0.26	0	0123210000
5	31	F	2/5/57	0	74	0.23	0	0011100000
5a	31	F	3/20/57	--	--	0.05	0	--
6	53	F	8/23/56	2	19	0.32	0.16	1222100000
6a	53	F	1/30/57	0	18	0.14	0.07	0121000000
7	30	F		3	37	0.48	0.10	4433200000
8	25	M		9	60	0.14	0	1453210000
9	24	F		3	27	0.25	0.06	0111000000
10	52	M		1	28	0.25	0.10	1122210000

nitely active. In 14 instances it was impossible to determine on clinical grounds alone what the activity of the disease might be.

The total CSF protein for all patients ranged from 9 to 83 mg. %, with a mean of 40 mg. %. The mean total protein for each of the subgroups was also 40 mg. %.

For the "inactive" group, of 17 patients (Table 2), the total CSF cholesterol ranged from 0 to 0.40 mg. %, with a mean of 0.17 mg. %. This mean did not differ significantly by statistical analysis from the mean normal total cholesterol of 0.11 mg. %. The free CSF cholesterol ranged from 0 to 0.06 mg. %, with a mean of 0.01 mg. %. Of the 17 patients in this group, 2 had free cholesterol present in the CSF. In the "questionably active" group, of 14 patients (Table 3), the total CSF cholesterol ranged from 0.05 to 0.46 mg. %, with a mean of 0.28 mg. %, which is significantly different from the mean normal total

TABLE 4.—*Cerebrospinal Fluid Cholesterol in Patients with Active Multiple Sclerosis*

Patient	Age	Sex	Date	CSF				
				WBC	TP	TC	FC	Colloid. Gold Curve
1	23	F		5	29	0.18	0	1222100000
2	9 mo.	F		--	35	0.65	0.45	--
3	36	M		--	51	0.55	0.16	0012110000
4	23	F	10/11/56	1	35	0.06	0	0001100000
4a	23	F	10/17/56	2	36	0.22	0	5554321000
5	35	F		8	38	0.60	0.50	0254320000
6	30	F		3	26	0.05	0	1222100000
7 *	33	F	8/28/56	2	34	0.16	0.08	5543210000
8	37	F		0	41	0.51	0.40	1122210000
9	6	M		0	9	0.29	0.06	0111000000
10	27	F	1/18/57	8	45	0.22	0.08	3533210000
10a	27	F	1/26/57	--	--	0.38	0.14	--
11 †	36	M	5/22/56	30	50	0.45	0.05	5554321000
12	34	F	2/6/57	14	40	0.31	0.18	0122100000
12a	34	F	3/22/57	0	47	0.23	0.11	0111100000
13	37	M		1	75	0.36	0.10	0122110000
14	40	M		2	41	0.21	0.07	0011000000
15	20	F		2	24	0.15	0.05	1122100000
16	50	M		4	37	0.25	0.12	0012210000

* See Patient 5, Table 2.
† See Patient 9, Table 2.

cholesterol. Free CSF cholesterol in this group ranged from 0 to 0.16 mg. %, with a mean of 0.04 mg. %. Seven of the fourteen patients had free cholesterol in their CSF.

In the "active" group, of 19 patients (Table 4), the total CSF cholesterol ranged from 0.05 to 0.65 mg. %, with a mean of 0.33 mg. %, while free cholesterol ranged from 0 to 0.50 mg. %. Of the 19 patients, 15 had free cholesterol in the CSF.

The four patients classified as "active," in whose CSF no free cholesterol appeared, were all for whom the exact time of onset of symptoms could be dated. For each the interval between onset of symptoms and lumbar puncture was less than 15 days.

An attempt was made to correlate activity with the presence of an increased number of leukocytes in the CSF. The finding of 6 or more leukocytes per cubic millimeter was considered abnormal. Correlation with colloidal gold curves was also attempted. The colloidal gold curve was considered to be abnormal if at least one tube gave a reading of 3 or more. In the "inactive" group, three patients had an increased number of cells and six had an abnormal colloidal gold curve. Of the two patients in this group who had free cholesterol in the CSF, one had both a positive colloidal gold curve and an increase in cells, while in the other both these tests were negative. In the "questionably active" group, three patients had more than 6 cells per cubic millimeter, and five had a positive colloidal gold curve. Of the seven patients with free CSF cholesterol, only one had a positive colloidal gold curve, while none had an increase in leukocytes. In the "active" group, four patients had an abnormal number of cells and five had a positive colloidal gold curve. All six of these patients had free cholesterol in the CSF.

Comment

Gmelin,[5] in 1826, was the first to demonstrate the presence of cholesterol as a component of brain tissue, and the substance was later repeatedly demonstrated to be a major constituent of myelin. Although the cholesterol normally present in myelin is predominantly in the free state, significant amounts of esterified cholesterol appear with demyelinization.[1,2,6]

The presence of cholesterol was first reported in CSF fluid from a patient with hydrocephalus by Schlossberger in 1851,[7] and in 1910 Mott [8] suggested that the presence of "lipoids" in the CSF were indicative of wasting of the nerve structures.

Investigations of CSF cholesterol before 1935 were critically summarized by Katzenelbogen.[9] This review and the studies since that time of four groups of investigators [10-13] have reported normal CSF total cholesterol ranges from a trace to 0.5 mg. %. However, all of these investigations were concerned only with determination of total cholesterol content, without differentiation of free and esterified fractions.

Selbach and Trappe [14] studied 48 CSF specimens obtained from patients suffering from a variety of psychiatric and neurologic illnesses. They reported a normal range between 0.05 and 0.24 mg. % of total cholesterol and found definite elevation of the total cholesterol value in a majority of cases of idiopathic epilepsy, schizophrenia, senile cortical atrophy, and gliomas located near the ventricular or subarachnoid spaces. They reported the free cholesterol-esterified cholesterol ratio as approximately 1:1 in all but two of their cases. Our present findings do not confirm the presence of as much free cholesterol in normal CSF. A probable explanation for the differing results lies in the use by Selbach and Trappe of an alumina (aluminum oxide) column for the fractionation of the CSF cholesterol. Aluminum oxide is known to hydrolyze esters, as noted by Trappe himself in an earlier paper.[15] Cerebrospinal fluid cholesterol esters may have been hydrolyzed during the analytical procedure, thus factitiously increasing the quantity of free cholesterol present.

Mandelboym, in 1955,[16] found free cholesterol present in 6 of 12 patients with post-traumatic epilepsy; however, in all 6, blood was present in the CSF, suggesting that the free cholesterol had been introduced with the admixture of blood. He also noted that the elevation of CSF cholesterol paralleled the elevation of the CSF protein.

A number of investigators in the past have been preoccupied with the origin of the CSF cholesterol. Two obvious sources have been suggested: an influx from the blood in cases of alteration of the blood-CSF barrier, or as a breakdown product of myelin in cases of destruction of neural tissue. Plaut and Rudy[17,18] carried out the most extensive investigations of this problem and concluded that in the normal no relationship existed between serum cholesterol levels and CSF levels. Coincident determinations of CSF cholesterol and of barrier permeability with the Walter bromide method showed that normal and low barrier permeability may result in high CSF cholesterol, while high barrier permeability may result in normal CSF cholesterol. They felt that the increase of CSF cholesterol was independent of the blood level and that it originated within the cerebrospinal cavity, being caused by metabolic disturbances in nerve tissue. On the other hand, Buchler[19] demonstrated that in all his cases in which cholesterol was found in the CSF, the barrier permeability, as tested by the bromide method, was found to be increased. In support of the possibility that the blood-CSF barrier permeability plays an important role in the accumulation of cholesterol in the CSF is the fact that meningitis or encephalitis of viral, pyogenic, or tuberculous origin is associated with significant elevation of the CSF cholesterol.[9]

Our finding that normal CSF cholesterol is 100% esterified cannot be explained at this time. If the absence of free cholesterol is not due to the limitations of our analytical procedure, we can only speculate upon the presence of an esterifying system existing somewhere between brain tissue and CSF or blood and CSF. That such a system does not exist in CSF itself is suggested by the fact that incubation of CSF for as long as one week at 37 C failed to alter the ester-free relationship.

Our results in infections and neoplasms of the nervous system agree with those of previous writers[9,11] in demonstrating a statistically significant relationship between the CSF total protein and the CSF free and total cholesterol fractions. Thus, in conditions characterized by elevation of the spinal fluid protein, determinations of spinal fluid cholesterol are of little value in evaluating the activity of the disease process.

In amyotrophic lateral sclerosis there is always a variable degree of demyelinization of the descending tracts in brain stem and spinal cord. It can thus be classified as a demyelinizing disease in spite of the fact that the primary site of disease is the motor cell. In the one patient we were able to follow for a long period of time, the period of apparent clinical *status quo* was characterized by a return of the total CSF cholesterol level to normal values and the disappearance of free cholesterol from the CSF. Resumption of clinical progression of symptoms was accompanied by a rise of the total cholesterol and the appearance of free cholesterol in the CSF. This would then be an instance in which the presence of free cholesterol in the CSF might be useful as an index of activity of the disease process.

The problem of objectively determining "activity" applies especially to multiple sclerosis and similar diseases. Efforts have been made to correlate cell count, total protein, and colloidal gold curves with clinical impressions of activity. Freedman and Merritt[20] summarized all these attempts by stating that "while the presence of an elevated cell count seems to be characteristic of the time of an exacerbation of multiple sclerosis, there is no clear evidence that any of the other noted abnormalities are related to the clinical picture." In 1954, Yahr,

Goldensohn, and Kabat [21] reviewed their experience with the immunochemical method for determining CSF γ-globulin and noted that levels of γ-globulin could not be correlated with the clinical picture. Roboz,[22] on the other hand, stated the contrary. Smith, Gerstl, Davis, and Orth [23] found that the presence or absence of CSF lipoproteins is without apparent relationship to the clinical state or other CSF findings in multiple sclerosis.

In our own group of cases, the presence or absence of free cholesterol appears to give a better correlation with the clinical picture of activity than the elevation of leukocytes or the colloidal gold curve. The fact that half of the patients classified as "doubtfully active," and 2 of the 17 patients classified as "inactive," had free cholesterol in the spinal fluid suggests that the presence of activity may be more accurately judged by this chemical determination; it also indicates that in certain patients the clinical signs and symptoms do not necessarily reflect the true state of the disease. We have not enough data as yet to estimate the significance of elevation of the total CSF cholesterol in the absence of free cholesterol. At this point only the presence of free cholesterol appears to correlate well with the clinical impression of the disease.

It should not be surprising that marked differences may occur in the absolute amounts of both esterified and free cholesterol found in the spinal fluid in multiple sclerosis at varying stages of activity of the disease. The size of lesions obviously varies widely, and there is certainly clinical evidence to suggest that "activity" may also vary considerably in rate and degree of intensity from patient to patient, or even at different times in a single patient. It is thus conceivable that in some situations no actual destruction of myelin takes place, but simple edema and functional disorganization. Such minimal activity will therefore not necessarily be shown in a method such as this one, which measures the appearance of products of myelin disintegration in the CSF. Minimal destruction of myelin—a situation perhaps best exemplified by the neuropathologic *Markschattenherde*—may result only in an increase of esterified cholesterol without the appearance of free cholesterol in the spinal fluid. It is also important to realize that a certain lag may exist between the onset of actual myelin destruction and the appearance of *Abbau* products in the CSF. Johnson, McNabb, and Rossiter [2] demonstrated, in their biochemical study of Wallerian degeneration, that it was not until after the eighth day that rapid changes occurred in the total cholesterol concentration and esterification of free cholesterol. The existence of a lag might help explain why in four of our cases definitely classified as active but of recent onset of symptoms, no free cholesterol could be detected in the CSF.

Therefore, it can be speculated that in multiple sclerosis and other primary demyelinizing diseases, the presence of free cholesterol in the CSF represents a breakdown product of myelin rather than an alteration in the blood-CSF barrier permeability. The presence of free cholesterol may thus be considered as an index of destruction of myelin, e. g., an index of the activity of the demyelinizing process.

Recent introductions of "disability scales" [26,27] are based on the presence or absence of objective signs, and activity is related to the appearance of new symptoms and signs within certain periods of time. This system does not, however, take into consideration the nature of the disease as judged from the pathologic point of view. A single minute lesion strategically located in the medial longitudinal fasciculus may give rise to a rather dramatic internuclear ophthalmoplegia, while a massive demyelinizing plaque involving the subcortical white matter of the frontal lobe may give rise to no symptoms except, perhaps, a rather subtle behavioral or emotional change. Thus, we judge the patient clinically by the signs and symptoms indicative of certain lesions, perforce ignoring the fact that other lesions

may be fully active, yet clinically silent. Exacerbations and remissions may well exist in this disease. It has been shown histologically that old, gliotic lesions may exist coincidentally with newer, fresh lesions; but in clinical practice, these terms reflect only partially what may be happening to the cerebrospinal white matter. An objective laboratory procedure for activity may reveal a somewhat different natural history for this disease. From the scant data accumulated to date, it would seem possible to speculate that, in addition to the classical cases with true, complete remissions and exacerbations—e. g., periods of active demyelinization alternating with periods during which the process is quiescent—there are cases in which active, slow, low-grade demyelinization occurs continuously, even though clinically the patient may appear to be in remission.

Cerebrospinal fluid cholesterol determinations are of little value as a diagnostic test for multiple sclerosis, even when CSF protein is within normal limits. Demyelinization is a nonspecific response of cerebrospinal white matter to many types of injury to the nervous system, and thus breakdown products of myelin, such as cholesterol, may appear in the CSF in a wide variety of conditions. It may be said, however, that the presence of free cholesterol in the CSF might be taken as a nonspecific index of parenchymal damage of the nervous system and employed in the same fashion as that in which the erythrocyte sedimentation rate is used in internal medicine to evaluate activity in rheumatic processes. In our own experience, in three cases, the diagnosis of conversion reaction was discarded after CSF examination revealed the presence of free cholesterol, and further investigation of the patient revealed the "organic" nature of the disease.

Summary

Free and esterified cholesterol was determined in the CSF, using a turbidimetric method for the estimation of digitonin-precipitable sterols.

Esterified cholesterol, but no free cholesterol, was found in the spinal fluid of normal controls.

In infections and neoplasms of the nervous system, the elevation of total- and free-cholesterol fractions was found to correlate with the elevation of the spinal fluid protein.

In amyotrophic lateral sclerosis, multiple sclerosis, and other similar demyelinizing diseases, the CSF cholesterol is independent of the level of CSF protein. The correlation between free CSF cholesterol and the clinical evaluation of activity of the disease would seem to indicate that the presence of free cholesterol may be useful as an objective index of activity of the demyelinizing process.

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Cortical and Rhinencephalic Electrical Potentials During Hypoglycemia

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Observations on EEG changes during insulin hypoglycemia were initiated by Hoagland et al.,[1] who noted the disappearance of alpha waves in schizophrenics subjected to insulin hypoglycemic treatment. Himwich and associates[2] found that the disappearance of the alpha waves occurred at the time the patient loses environmental contact. In a series of observations on dogs, Hoagland and co-workers[3] reported that subcortical waves continued after the cortical undulations had disappeared. Differences between cortical and subcortical electrical activity in hypoglycemic rabbits have also been disclosed in the work of Tokizane and Sawyer,[4] who observed seizure patterns in subcortical areas, i. e., amygdala and hippocampus, when the cortical recordings were devoid of such hyperactivity. Further analysis of the differential cortical and subcortical electrical potentials of cats made by Fernández and Brenman[5] revealed that the auditory cortex retained the evoked response to the click stimulus even in very pronounced hypoglycemia, induced either by evisceration or insulin. In the present experiments the comparative analysis of cortical and subcortical activities has been extended to include responses produced either by pain or by visual stimulation.

Method

Our experiments were performed on New Zealand albino rabbits weighing approximately 3 kg. Twenty-four hours before the experiments were initiated the animals were deprived of food, but not of water. On the evening of the same day they received 10 units of protamine zinc insulin intramuscularly. On the following morning the rabbits were usually found in deep hypoglycemia, and in many instances had suffered convulsive seizures. In order, however, to maintain the condition of profound hypoglycemia, hourly intramuscular injections of 40 units of regular insulin were initiated and continued for the remainder of the experiment, with periods which varied from 4 to 11 hours in the various animals. The rabbits were then given minimal amounts of pentobarbital sodium, either 15 mg. i. v. or 60 mg. i. m., to prevent motor activity during the operative procedures. The effects of the light barbiturate anesthesia were exhausted early in the experiment. A tracheotomy was performed, and the animals were placed under artificial respiration to facilitate breathing during the medullary phase of hypoglycemia. The skull of the rabbit was trephined, and the stereotaxic coordinates were established according to the method of Sawyer and associates.[6] Coaxial needle electrodes were prepared by filing the shaft of a 16-gauge hypodermic needle to a length of 2.0 mm. A small piece of polyethylene tubing was then inserted into this shaft and trimmed to fit flush with it. A No. 24 enamel-insulated copper wire was inserted into the polyethylene-insulated shaft and fixed to the needle by means of dental acrylic. The wire was cut to the appropriate length: 15.5 mm. for the amygdaloid leads, 5.0 mm. for the hippocampus, and 12.0 mm. for the midbrain area. The shaft of the needle and the copper electrode recorded from the cortex and subcortex, respectively. EEG tracings were taken from the motor, limbic, and occipital cortices and the amygdaloid, hippocampal, and midbrain areas. Bilateral recordings were made, and the placement of electrodes was later confirmed by histological examination. Painful stimuli were produced by pinching the foot of the rabbit. A Grass photic stimulator effected visual stimulation, the photo element being placed approximately 20 cm. from the eye of the rabbit. All recordings were made with a Grass Model III ink-writing electroencephalograph. Blood sugar determinations were made by the method of Somogyi, as modified by Nelson.[7]

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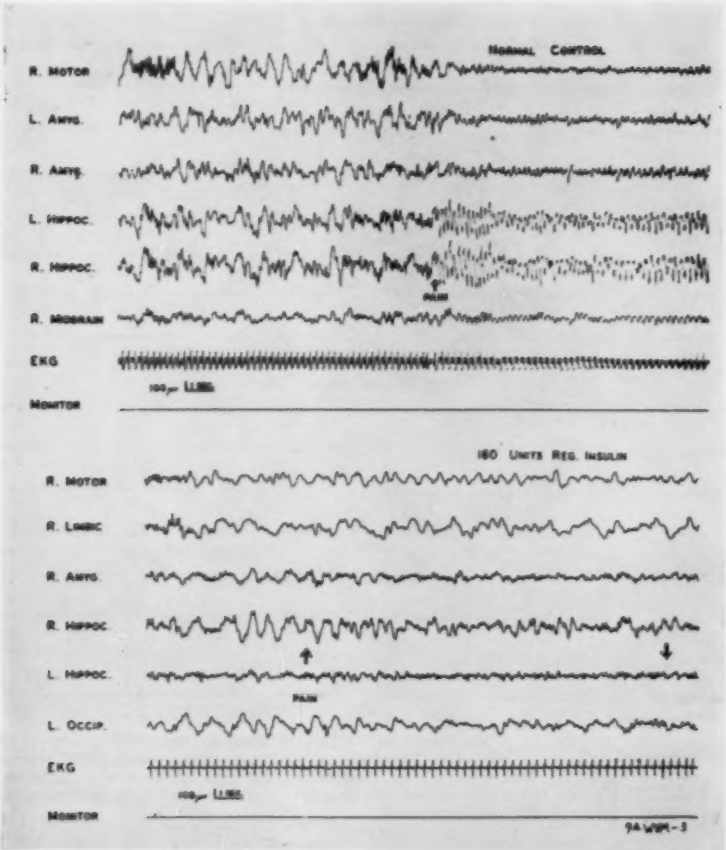


Fig. 1.—Failure of arousal response after painful stimulation (lower group of tracings) as compared with normal response (upper group of tracings). Abbreviations employed in this and in subsequent figures are as follows: *R.* or *L. Motor*, right or left motor cortex; *R.* or *L. Limbic*, right or left limbic cortex; *R.* or *L. Occip.*, right or left occipital cortex; *R.* or *L. Amygd.*, right or left amygdala; *R.* or *L. Hippoc.*, right or left hippocampus; *R.* or *L. Midbrain*, right or left midbrain area; *EKG*, electrocardiogram; *Monitor*, monitor deflection indicating photic "flash" stimulation.

Note that the normal response to pain disappears during hypoglycemia.

Results

In accordance with previous works,[2,3] we noted that as the animals progressed through the various phases of hypoglycemia, as described by Himwich,[8] there was a lowering of the amplitude of the EEG potentials in all leads. This decline gradually continued until all EEG activity apparently ceased. However, two animals suffered a series of tonic and clonic seizures, lasting for 5 to 15 seconds, prior to the "black-out" of the EEG pattern, and in three other animals subcortical spiking was observed in all leads just before the disappearance of the spontaneous EEG activity.

Evoked Responses to Painful and Visual Stimulation.—The first change in the electrical recordings during hypoglycemia was noted in the failure of the alerting response to painful stimuli, the cortex being more susceptible than the subcortex. The loss of the arousal reaction was observed in each of the 20 observations made (Fig. 1). Next in order of elimination were the waves of

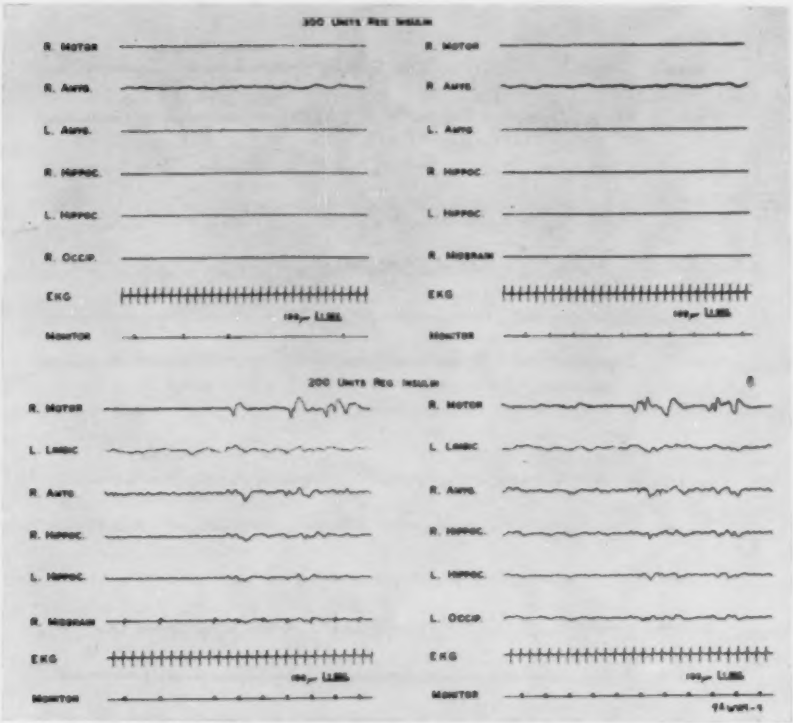


Fig. 2.—Four groups of brain waves of rabbits in deep hypoglycemia. The upper two groups represent failure of response to photic stimulation during medullary phase. The lower group of tracings was obtained by repeatedly switching from midbrain to occipital cortex leads. The lower left group shows response to visual stimulation in midbrain, whereas occipital cortex (lower right) fails to react.

the spontaneous EEG. On the other hand, the reaction to visual stimulation, both in the occipital cortex and in the midbrain region, persisted a longer time. Either the evoked responses in the occipital cortex disappeared prior to that in the midbrain (Fig. 2) or both were extinguished at approximately the same time. In none of the instances did the occipital cortex register a reaction to light after the response in the midbrain had been extinguished. Finally, all evoked responses, whether to pain or to visual stimulation, disappeared, and the tracings became flat.

Tonic and clonic seizures usually developed early in insulin hypoglycemia, and such behavioral changes were observed whether or not spontaneous EEG activity was still present. These seizures were sometimes preceded by subcortical spiking in the hippocampus (right and left) and/or the amygdala (right and left) (Fig. 3). Such subcortical activity could occur after the spontaneous EEG was no longer present in cortex or subcortex. Seizure discharges limited to the hippocampus and amygdala were not associated with motor activity (Fig. 4). When the discharge was initiated in the hippocampus, it might extend to the amygdala and vice versa. There was a progressive type of spike-like activity which spread to the cortex from subcortical structures (Fig. 5). The order of regression of the convulsive brain waves was the reverse, as the tracings disappeared first from the cerebral cortex and later from the amygdala or hippocampus. Blood samples were collected from eight hypoglycemic ani-

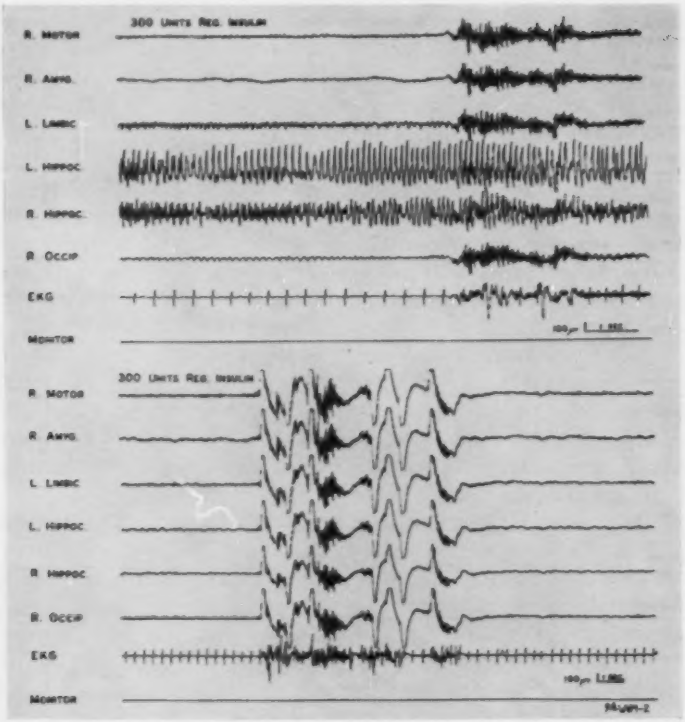


Fig. 3.—Tonic and clonic seizures preceded by hippocampal activity in the upper group of tracings and appearing simultaneously in all leads in the lower group of tracings. Muscle potentials mask the brain waves, but the absence or presence of subcortical activity prior to the seizure is apparent.

mals, and the blood was analyzed for glucose, yielding values from 7.6 to 47.0 mg. %, with an average of 24.5 mg. %.

Comment

The temporal order of depression of the cerebral electrical activity began with a loss of the alerting response to pain. Comparisons were made between the cortical areas and the hippocampus, amygdala, and midbrain areas during pain stimulation. The results indicated that the subcortical structures were more sensitive to arousal stimulation than the cortex during hypoglycemia (Fig. 2). In light of the work of Green and Arduini,[9] this is not surprising, as they found varying EEG patterns in neocortex and hippocampus. In records of spontaneous activity, the hippocampal recordings might be synchronized, while those of the neocortex were desynchronized. The reverse phenomenon was also observed. French et al.[10] found that direct stimulation of the reticular formation ceased to evoke a discharge during hypoglycemia at a time when the cortex was still responsive. In our experiments we have also noted the alerting reaction which includes the functions of the reticular formation to be the most susceptible to depression during hypoglycemia.

After the loss of the arousal reaction, the spontaneous EEG failed. Next followed the visual responses, which disappeared either first from the occipital cortex and then from the midbrain or from both these areas at apparently the same time.

Like Tokizane and Sawyer,[4] we found that hypoglycemia spike discharges might

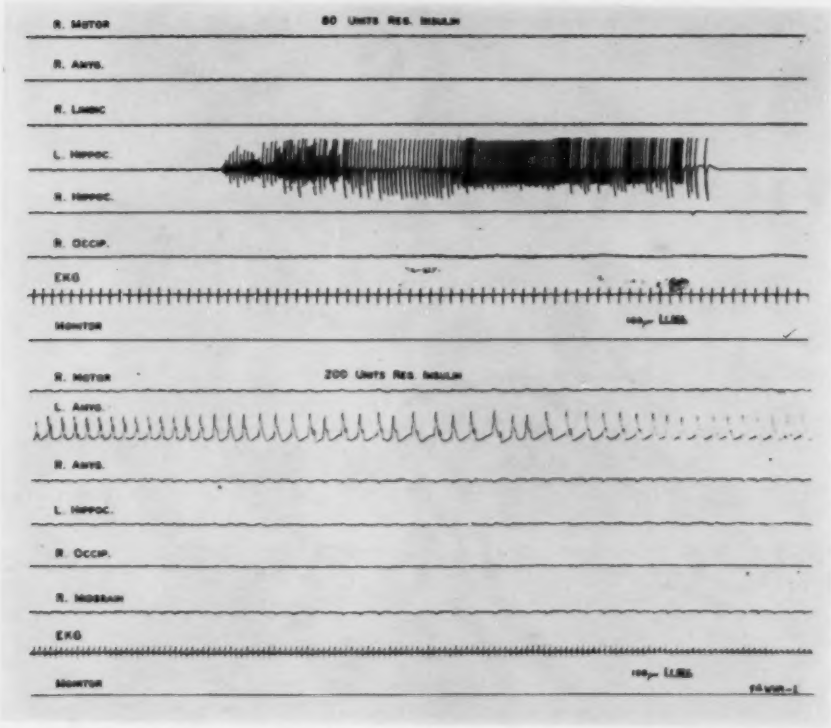
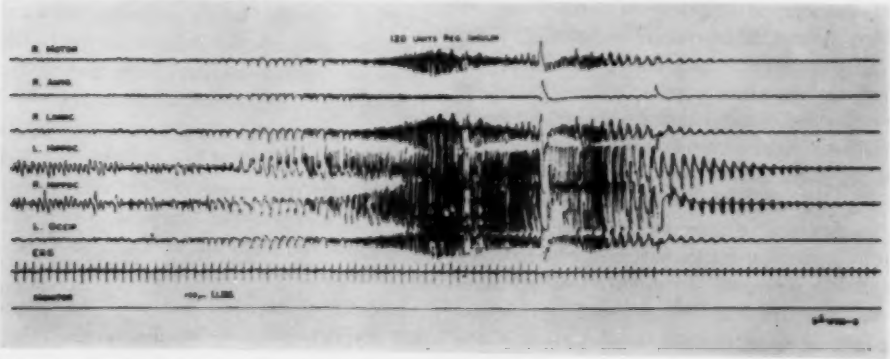


Fig. 4.—Hypoglycemic spike discharges confined to the left hippocampus (upper group of tracings) and left amygdala (lower).

be initiated in the hippocampus and/or amygdala and that these patterns were not accompanied by motor hyperactivity. The susceptibility of the rhinencephalon to seizure discharges has been described by Liberson and co-workers [11,12] and Green et al.[13] They noted that the hippocampus had a low epileptogenic threshold and was therefore involved in the initiation of convulsions produced by electroshock. Liberson et al.[12]

Fig. 5.—Progressive hypoglycemic seizure pattern. Note the onset in the hippocampi and extension to amygdala and to various cortical leads. Finally, the seizure pattern regresses.



also reported that with spike patterns limited to the amygdala and/or hippocampus there was little, if any, associated motor activity. Unlike Tokizane and Sawyer,[4] however, we did not observe that the convulsions resulting from hypoglycemia were invariably initiated subcortically. Rather, we frequently found seizure onsets appearing in all leads simultaneously (Fig. 3). Unfortunately, muscle artifacts accompanied this convulsive hyperactivity and made it impossible to say that motor activity was definitely associated with convulsive cortical patterns. However, the investigations of Andy and Akert,[14] Preston,[15] and the Killams [16] revealed that unless the motor cortex was involved, muscular hyperactivity failed to develop.

Our results with the electroencephalograph suggested a decreasing metabolic gradient parallel with the disappearance of electrical activity. The order in which the various cerebral electrical activities were depressed indicates that they have quantitatively different metabolic demands. It would seem, therefore, that the maintenance of the alerting reaction would have the greatest energy requirement. This complex reaction involved functions of the collaterals from the lemnisci to arouse the midbrain reticular formation, which, in turn, stimulates the diffuse thalamic nuclei to send impulses to all parts of the cerebral hemispheres, resulting in a desynchronous electrocorticogram. It is therefore not surprising that this reaction would require so much energy. One step lower are the energy demands for the functions of the spontaneous electroencephalogram. This activity is also widespread in the brain. In view of the metabolic gradient of the brain, which decreases down the neuraxis from a rostral to a caudad direction,[8] it is not surprising that the subcortical waves were present when potentials from the cortex could no longer be observed. In our experiments, the response to visual stimulation was the most tenacious. However, that, too, was eliminated as the depth of hypoglycemia increased.

Fernández and Brenman [5] reported that a click stimulation evoked a response from the auditory cortex in cats, despite a hypoglycemic condition in which blood sugar levels were as low as 5 mg. %. Their animals were probably in the medullary phase of hypoglycemia. This phase is critical, and if brain metabolism is not rapidly restored by dextrose, may result in irreversible damage. It is therefore conceivable that the potential induced in the auditory cortex could be maintained either by the brain consuming its own substance or by a supply of exogenous energy which is less than that required for the evoked visual response. Such a utilization of brain structure may be similar to the phenomenon disclosed by Abood and Geiger,[17] who perfused the brain with an aglycemic blood substitute. In an effort to obtain more information, one might attempt to restore brain functions by the administration of dextrose. Failure of restoration would indicate that brain destruction had occurred. Whether or not the brain utilizes its own constituents to maintain the auditory response, its energy requirements are probably of a low order.

Clinical experience has indicated the value of Sakel's insulin hypoglycemia therapy for patients with schizophrenia.[18] Even though this treatment has been used for many years, we still do not understand its mechanism of action. This analysis of the electrical activity of cortical and subcortical areas of rabbits subjected to profound insulin hypoglycemia suggests a possibility for the therapeutic action. It is now recognized that the Papez circle [19] represents an important part of the anatomic substrate of the brain for the emotions. The prominent role played by the amygdala, and especially by the hippocampus, in the maintenance of the convulsive activity and the knowledge that these two areas are included in the anatomic substrate of emotion suggest that hypoglycemia produces its therapeutic effects by interfering with these

two rhinencephalic structures and thus perhaps altering the functions of the Papez circle.

Summary

Twenty albino New Zealand rabbits, each weighing approximately 3.0 kg., were subjected to profound insulin hypoglycemia. Spike discharges were observed in the hippocampus and/or amygdala unaccompanied by any apparent somatic motor hyperactivity. Behavioral convulsions were seen either preceded by spikes in the hippocampus and/or amygdala or appearing simultaneously in all leads. The recession of electrical activity usually occurred in a pattern. The alerting reaction to pain was extinguished first, the cortex usually displaying greater susceptibility than the subcortex. Then came, in order, spontaneous EEG activity and the evoked response to visual stimulation in the occipital cortex and in the midbrain area. However, sometimes both responses to visual stimulation disappeared at approximately the same time. Finally, all brain-wave activity disappeared, and the tracings became flat.

The susceptibility of the amygdala and hippocampus, which are always involved in hypoglycemia seizure patterns, whether or not they also take place in the cerebral cortex, suggests that the mechanism of the therapeutic action of insulin hypoglycemia includes a change in rhinencephalic function.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Irving C. Sherman, M.D., President
Oscar Sugar, M.D., Secretary

Regular Meeting, May 21, 1957

Hepatolenticular Degeneration (Wilson's Disease). DR. BENJAMIN BOSHES.

I should like to present two cases of hepatolenticular degeneration (Wilson's disease), those of a brother and a sister who have been on dimercaprol (BAL) treatment, the brother for six years and the sister for five years. A., the brother, was completely helpless, burdened down by tremor and other associated movements, so that for months on end he could not have a haircut or a shave. He was unable to write. I shall project on the screen specimens of his handwriting before and after the dimercaprol treatment. On a few occasions, to rule out the effects of suggestion, we gave him peanut oil injections instead of the dimercaprol in the peanut oil. Within a week or two, symptoms had recurred, and he would return with the complaint that he was "not getting any benefit out of the medication."

I should like to show some of the subtleties of this illness. The sister was sent to me because she had developed an anxiety state following a fourth miscarriage. At first she said her family history was negative, but when I examined her, I noticed Kayser-Fleischer rings. This prompted me to ask her again about the family history, and then she admitted that she had a brother who was nervous. Closer questioning about the brother revealed that he was a patient at the Veterans' Administration Hospital at Hines, on Ward 50-A, actually my ward. When I asked her the name, she gave it. B., the sister, was married; so there was no similarity of names.

Both these patients have been receiving 2.5 mg. of dimercaprol per kilogram of body weight one day per week, four injections at six-hour intervals.

I shall ask Dr. Bernsohn to discuss the copper findings in these cases which have been followed over several years. I might add parenthetically that A. has been working for the past several years as a packer and has had no difficulty in holding his job.

Discussion

DR. J. BERNSOHN, Hines, Ill. (by invitation): In 1930 Haurowitz found the copper content of brain and liver increased in a case of hepatolenticular degeneration, and this was confirmed by Cumings in three cases. Increased urinary copper excretion in this syndrome was reported by Mandelbrote and co-workers, and by Porter; Denny-Brown then treated affected patients with dimercaprol, and it was his observation that this disease constitutes another in the series of metabolic disorders classified by Garrod as "inborn errors of metabolism."

I should like to consider the etiologic factor in this disorder. In 1948, Holmberg and Laurell isolated a copper-containing protein in serum, which they called ceruloplasmin, and in 1952 Scheinberg and Gitlin showed that this copper proteinate was low in the serum of patients with hepatolenticular degeneration. Ceruloplasmin is a blue α-globulin, with a molecular weight of 150,000, and contains eight atoms of copper per molecule. Its concentration in normal serum is about 25-30 mg/100 ml., and it constitutes about 0.5% of the total serum proteins. Ceruloplasmin has oxidase activity toward aromatic amines, among other substrates. It is known that in hepatolenticular degeneration there is an increased absorption of copper from the gastrointestinal tract, and the idea has been advanced that the clinical signs in this disorder are due to the increased deposition of copper in the tissue due to the increased absorption. This is manifested in the renal damage, which then produces a γ-aminoaciduria because of defective resorption by the tubules. The liver damage and basal ganglia degeneration are also explicable on the same basis. Another theory of the etiology is that there is a defective synthesis of ceruloplasmin in hepatolenticular degeneration, which is the "inborn error of metabolism," and the protein cannot perform its physiological function adequately. A third concept has been advanced by Uzman that in hepatolenticular degeneration the liver proteins have an avidity for copper, leading to high concentrations in that organ and accounting for the low serum ceruloplasmin.

Porter and Folch have recently shown that there is present in the brain copper proteins, in hepatolenticular degeneration, an abnormal fraction, from

which the copper can be dialyzed under certain conditions.

A word about the Kayser-Fleischer ring: Uzman and Jakus have recently demonstrated that in the cornea of a patient with hepatolenticular degeneration a large amount of copper was deposited throughout the substantia propria. The copper here was in a different form from that in the Kayser-Fleischer ring. It was alcohol-insoluble but easily removed with edathamil (Versene) and dilute mineral acids. The presence of large amounts of copper throughout the substantia propria did not seem to affect the color of the optical properties of the cornea. Examination of the Kayser-Fleischer ring itself indicated that the copper was localized within fine granular deposits in Descemet's membrane. The deposits were arranged in two parallel zones of unequal width, close to the endothelial surface of the membrane and separated by a clear layer. The data would indicate that the copper present in the Kayser-Fleischer ring is not in the form of copper salts but exists as a copper chelate.

We have studied a patient with hepatolenticular degeneration for one year, during which time we determined urinary copper prior to, during, and after dimercaprol administration once a week. He excreted 300μg.-500μg. of copper per day; this dose was increased initially three- to fivefold on the days on which he received dimercaprol. However, as time went on, the response to dimercaprol diminished, until toward the end of the year only a minimal response to dimercaprol was evident. From this we concluded that the stores of copper in this patient were being depleted, and this supposition coincided with the absence of any progression of the neurologic symptoms.

DR. ALEX ARIEFF: I wish to ask a question. I take it the patients are still on dimercaprol. How often do you give it, and how do you judge the doses from now on?

DR. BENJAMIN BOSHES: Both patients are on the same dosage, 2.5 mg. per kilogram of body weight, and they will not permit us to take them off the drug. In the beginning, we took A. off dimercaprol and put him on peanut oil, but he came back and said the "BAL was not working"; so we put him back on peanut oil containing the drug. He is getting it once a week, four times a day.

DR. JOHN S. GARVIN: It is extremely interesting that these patients had an exacerbation when taken off dimercaprol. We have had patients at the University of Illinois who have shown a good response to this drug and then relapsed if we did not keep them on it. We have also used penicillamine. When patients had reactions to dimercaprol, we substituted penicillamine and achieved an excellent response in about two weeks after instituting therapy.

Progressive Muscular Dystrophy of the Extraocular Muscles. DR. WALTER R. KIRSCHBAUM.

A 35-year-old white man with a negative family history manifested in the early teens bilateral ptosis of the eyelids. A complete external ophthalmoplegia developed in the following years and has remained stationary since. The case represents the ocular type of progressive muscular dystrophy. A nuclear amyotrophy is definitely ruled out by the preservation of the motor end-plates in the severely degenerated fibers of the external eye muscles, as demonstrated by biopsy. Electromyographic examinations were not conclusive, owing to the far-advanced myodegeneration. Biopsy specimens taken from the midportion of the eye muscle established the diagnosis.

Regulation of Carbohydrate Metabolism in Patients with Injuries to the Spinal Cord. DR. MEYER BROWN, DR. JOSEPH BERNSOHN, and DR. JOHN FINKLE.

For several years we have been making studies of the defects in regulatory mechanisms of autonomic functions which have followed injuries to the spinal cord. In the present investigation we are concerned with the effects of spinal cord injury on the regulatory mechanism of carbohydrate metabolism. We studied oral glucose tolerance curves in 39 patients with injuries to the cervical portion of the spinal cord, 30 patients with injuries to the thoracic portion, 17 with injuries to the lumbar portion of cauda equina, and 17 normal subjects, for control purposes. We also studied intravenous dextrose tolerance curves in another 11 patients with injuries to the cervical portion of the cord and in 12 patients with injuries to the cord at or below the 11th thoracic segment. Insulin tolerance curves and the dextrose response to injected epinephrine were also investigated in the same two series of 11 and 12 patients.

We found that patients with injuries to the cervical portion of the spinal cord had abnormally high and sustained oral glucose tolerance curves as compared with patients with injuries to lower portions of the spinal cord. However, intravenous dextrose tolerance curves and insulin tolerance curves were substantially the same in patients with cervical cord injuries when compared with patients having an injury to the lowermost segments of the spinal cord. A difference exists in the last two groups with respect to the effect of injected epinephrine. We found that injection of epinephrine produced a significantly smaller rise in the blood sugar value in patients with cervical lesions than in patients with lesions from Th11 downward.

The meaning of these findings is discussed.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Abner Wolf, M.D., President, New York Neurological Society, Presiding

Joint Meeting, April 9, 1957

Spontaneous Return of Function Following Surgical Section or Excision of Seventh Cranial Nerve in Surgery of Parotid Tumors.

Dr. Hayes Martin and Dr. James T. Helsper.

In a consecutive series of 543 patients with parotid tumors operated upon on the head and neck service of Memorial Hospital during the years 1949 to 1953, inclusive, the seventh nerve was found to perforate the tumor, leading to elective sacrifice of at least 2.5 cm. of the main trunk and the branching plexus, in 40 patients. Twelve of these patients have developed massive recurrence or have died within a year. The remaining 28 patients make up the basis for this report. In no patient has any form of nerve graft or other neurorrhaphy been done. In eight patients (28.5%) there has been a definite return of function (active motion) in the paralyzed side of the face. The mechanism and clinical significance were discussed.

Discussion

Dr. James B. Campbell opened the discussion of this paper.

Dr. George H. Hyslop: We know that the trigeminal in its third branch carries motor fibers. We know that the facial nerve carries deep sensation, as well as some taste fibers via the chorda tympani.

From 1922 to 1926 I corresponded with Dr. Loyal Davis about certain unusual instances of lower-neuron complete facial paralysis arising in the course of either mandibular division involvement in tooth infection, with or without osteomyelitis, or of block of the inferior alveolar or dental nerve, cutting common sensation. In the cases related to nerve block, the facial paralysis occurred anywhere up to 10 hours after the procaine injection. The paralysis was usually brief, but in some instances function was not recovered. Dental surgeons are not surprised when this does happen.

Dr. John J. Conley: I have had a few experiences in cutting the facial nerve that I have not been able to explain. From 1951 to 1953 I carried out seven nerve grafts, and the results were fairly satisfactory. Of the seven patients, two had good return of function; two had fair; one had poor, and two were failures. So even with a nerve graft we cannot assume we will get a good result. However, as a result of my experience with nerve grafting, I came to the conclusion very early that things were happening in the facial nerve that I could not explain.

Dr. Hayes Martin: Most of you know that neither Dr. Helsper nor I is a neuroanatomist or neurosurgeon, and I think, therefore, that we should not insist upon the acceptance of our explanation of this phenomenon. The fifth nerve seems to us the most reasonable channel for the reestablishment of pathways for conducting new motor impulses to the facial muscles. Certainly this possibility should be investigated further.

From my discussions with neurologists and neurosurgeons, I get the impression that it is very difficult for the average neurologist to accept the possibility that the fifth nerve can carry motor impulses to all parts of the face.

I trust that further investigations will be carried out by those who are competent in neurophysiology and neuroanatomy in the attempt to explain this phenomenon. We would be grateful to anyone who will undertake this, and, within reason, we would ask our patients to lend themselves to further examination and investigation.

Experimental Gliomas and their Significance for the Classification of Human Brain Tumors.

Dr. Harry M. Zimmerman.

The attempt to reproduce the different types of gliomas known in man succeeded with a variety of chemical carcinogens which were implanted in the brains of certain strains of mice. These tumors could not be produced in dogs, rabbits, and guinea pigs, but to a very limited degree their induction was successful in rats. By these experimental means, tumors were produced of the astrocytic, astroblastic, glioblastomatous, ependymomatous, medulloblastomatous, oligodendrogliomatous, and polar spongioblastic varieties. Their common sites of predilection in the brain of the mouse are the same as in man. The production of these experimental tumors at will in relatively large numbers has permitted detailed analyses of their cytogenesis. Such studies have demonstrated that gliomas represent mixed neoplasms of cytologically distinct origins. This is not to deny, however, that in any particular glioma the progeny of one cell of origin may predominate numerically or influence the rate of growth of the tumor as a whole. In the last analysis it is these factors, i. e., numerical superiority and rate of growth, which determine the classification of the tumor.

Discussion

DR. J. LAWRENCE POOL: I have enjoyed this paper tremendously, as have all of us who have followed Dr. Zimmerman's work. I would like to ask, first, whether he is able to differentiate human glial tumors by this technique. Secondly, does Dr. Zimmerman's work help explain the susceptibility of certain glial tumors to x-ray therapy and the nonsusceptibility of others of the same apparent histologic character?

DR. HARRY M. ZIMMERMAN: I have had occasion to examine carefully the entire periphery of a so-called glioblastoma and have found portions of it which looked like oligodendroglioma and portions like astrocytoma. In such a tumor, if the surgeon removes the part that looks like astrocytoma and gives that to the pathologist, the latter will make an incorrect diagnosis. Many of these human glial tumors are mixed, and sometimes the cells produce different patterns in different parts of the tumor.

The most benign glioma, the astrocytoma, responds moderately well to irradiation. By experience only have we come to realize that certain gliomas respond well or moderately well, and that other tumors do not respond at all. In mouse tumors the same thing happens. We worked with astrocytoma in transplantation experiments, irradiating these tumors and causing their disappearance to palpation. It then takes many months for them to recur, if they recur at all. We have irradiated ependymomas with 5000 r in one dose, causing but a transient disappearance of these tumors, followed by a prompt regrowth, so that at the end of four weeks they were as large as the nonirradiated gliomas in the control animals. Experimentally, as in man, we find that the response of gliomas to x-radiation is variable; but that does not quite answer your question, for I still do not know why it is so.

DR. J. LAWRENCE POOL: I am greatly interested in your statement that x-ray therapy is of benefit in human cases of astrocytoma; is that correct?

DR. HARRY M. ZIMMERMAN: Yes.

DR. J. LAWRENCE POOL: And perhaps not so much in glioblastoma multiforme?

DR. HARRY M. ZIMMERMAN: I will say again that astrocytomas in our hands are among the gliomas that respond best to x-radiation, and that we have had very bad results with glioblastoma multiforme. I wonder whether the old question of misdiagnosis does not enter into this, because since many of the tumors are mixed, it is possible to take out a portion which looks astrocytomatous, and is so diagnosed, whereas the bulk of the tumor is a glioblastoma multiforme.

Studies on Vascular Encephalomalacia: Evaluation of Clinical Syndromes in Five Hundred Consecutive Cases Studied Pathologically. DR. STANLEY M. ARONSON and DR. ABRAHAM M. RABINER, Brooklyn.

The autopsy records of a large general hospital were analyzed in regard to the incidence, topographic distribution, and disease association of 500 consecutive cases of vascular encephalomalacia. The crude rate of encephalomalacia increased with age; it was noted in 16% of all autopsies on patients below the age of 15 years and in 59% of persons dying beyond the age of 75. Many of the lesions were clinically unrecognized, this percentage increasing with advancing age. Encephalomalacia as a cause of death reached a peak in the fifth decade of life and then declined relatively. Hypertension was intimately associated with encephalomalacia, particularly after the age of 35. The presence of hypertension increased the probability of cerebral infarction twofold. Diffuse arteriolar sclerosis was often the cause of a disseminated pattern of multiple malacia, with a characteristic clinical representation. Heart disease was present in the majority of cases analyzed. Diabetes mellitus also was a concomitant feature and had its most striking effect upon those zones of intracranial tissue serviced by direct perpendicular perforating arteries (basal ganglia and pons), where the results of accelerated atherosclerosis would be most prominently displayed.

The factors enhancing certain regional patterns of encephalomalacia were outlined.

Discussion

DR. H. HOUSTON MERRITT: The series reported by Dr. Aronson and Dr. Rabiner, 500 cases, is probably the largest in the literature, and we are all grateful to them for bringing these data before us. I do not think that they need to be too concerned about the high incidence of encephalomalacia (15%) in children. The vascular lesions in these children were perhaps related to rheumatic heart disease and similar conditions. With the decreased death rates in children from the acute pyogenic infection, there must be a rise in the percentage of conditions which were formerly relatively rare, and for which we have not, as yet, any effective therapy.

DR. MORRIS B. BENDER: I should like to ask about the incidence of red infarct in patients with encephalomalacia of the brain. My other question is this: The authors did not say much about hemorrhage; they were talking about encephalomalacia. But they did show a graph in which hemorrhage of the brain was present, but this was surprisingly low in the old-age group. To be able to diagnose hemorrhage of the brain is another

problem. It is so easy if there is blood in the spinal fluid; but the question comes up: How often does one see hemorrhage in the brain when the spinal fluid is normal?

DR. J. LAWRENCE POOL: I should like to ask the authors how many cases they have had of Parkinson's syndrome which showed spotty vascular lesions in the basal ganglia, like those illustrated in your slides. To those of us who are interested in surgery of the globus pallidus, this is a matter of considerable interest.

DR. STANLEY M. ARONSON: In answer to Dr. Bender's question concerning the incidence of red infarcts: I presume he means by this term vascular insufficiency with secondary hemorrhagic diapedesis. It is fairly frequent in those lesions which we feel can be accounted for by embolic closure of a vessel, particularly in those lesions, embolic or otherwise, which seem to involve the cerebral cortical mantle.

With reference to the question of cerebral hemorrhage: The graph represented merely the number of cases of coexistent cerebral hemorrhage in instances of discrete encephalomalacia and did not represent the actual incidence of spontaneous cerebral hemorrhage at Kings County Hospital.

I do not have our data concerning Parkinsonism with me, but I should like to point out one case which comes to my mind, that of a patient with Parkinsonism for about 10 years who died of some extracerebral cause, the nature of which I do not recall. At autopsy the patient had lesions in the mesial aspect of the globus pallidus bilaterally. One would have imagined that the patient should have spontaneously cured herself, and yet a careful evaluation of the clinical chart showed no reversal in her paralysis agitans; in fact, if anything, it became progressively worse in the terminal years of her life.

Surgical Approach to Treatment of Uncontrolled Seizures in Patients with Infantile Hemiplegia. DR. JOSEPH RANSOHOFF and DR. SIDNEY CARTER.

Hemispherectomy in the treatment of certain patients with uncontrollable seizures is presented.

These patients must meet the following criteria in order to be considered for this operation: 1. *Infantile hemiplegia,* which occurred within the first two years of life, and is associated with underdeveloped extremities and a hemisensory syndrome and may or may not be associated with hemianopsia. 2. *Uncontrollable seizures,* not necessarily focal, although most have some focal component. 3. *X-ray changes* in the plain skull films and air studies indicating an underdeveloped and atrophic hemisphere, namely, a small hemicranial cavity with thickening of the bone and enlargement of the air spaces on that side and a dilated ventricle with displacement of the normal brain toward the dilated, atrophic side. 4. Most of the patients have severe *personality disorders* of a destructive and antisocial nature, this often being the factor which forces the parents to seek operative help.

Electroencephalographic findings are of little aid, since the tracings from the normal side will mirror those from the abnormal one prior to operation; in the postoperative period the normalcy of the remaining brain will become evident from the electroencephalographic tracings.

Eleven patients were presented as having been treated by hemispherectomy, two dying approximately six months postoperatively, with high temperatures that were unexplained at autopsy. One patient died six weeks postoperatively of uncontrolled seizures and was considered to have been a case of poor selection. Three hemispherectomies were on the right side and eight on the left side. The eight surviving patients are doing very well; six have had no seizures since operation, and of these, three are on small doses of anticonvulsants, which are being reduced, and three are completely off all anticonvulsant medication. The two remaining patients are on small doses of anticonvulsants in order to control occasional seizures. There were no instances of loss of motor or speech function, and all patients showed a remarkable improvement in personality disorders, enabling considerable social rehabilitation.

Discussion

DR. H. HOUSTON MERRITT: Dr. Ransohoff has clearly defined the indications for hemispherectomy, and there is little for me to add. I am sure that most of us had difficulty in believing the early reports that removal of an entire hemisphere did not increase the degree of disability in a patient with infantile hemiplegia. The work of Dr. Ransohoff and his colleagues indicates that these reports are true. Those of us who have seen these cases certainly can confirm the report that the removal of the diseased hemisphere does not increase the motor deficit, and does not bring on an increased sensory deficit, except for the visual one. This is understandable when one considers the fact that gross movements of the trunk, legs, and arms are bilaterally innervated, and in these patients with a severe lesion on one side, the movements on the paralyzed side are probably controlled by the homolateral hemisphere.

With regard to the convulsive seizures, Dr. Ransohoff's data clearly show that when diseased brain tissue that is producing fits is removed, the convulsive seizures will cease.

Dr. Ransohoff's remarks in regard to the electroencephalogram are very interesting. Before the operation in these patients there is abnormal activity in both halves of the brain, and if you were not told the history it might be difficult to determine which half of the brain was most diseased.

It is interesting that the mentality of these patients is not particularly affected by the operation. Their I. Q. does not deteriorate or improve. It would seem logical to think that it might improve, if the normal hemisphere is relieved of the disturbance produced by the diseased hemisphere; but this does not seem to happen.

PHILADELPHIA NEUROLOGICAL SOCIETY

Harvey Bartle, M.D., Presiding

Regular Meeting, April 5, 1957

Evaluation of Meprobamate (Miltown) Therapy in Various Neurological Disorders. Dr. Richard W. Naef (by invitation), Dr. Nathan S. Schlezinger, and Dr. Winslow J. Borkowski.

Meprobamate (Miltown) was reported by its manufacturers to have muscle-relaxant, anticonvulsant, and sedative effects on experimental animals. To evaluate these effects clinically, the drug and identical placebo tablets were used in a controlled therapeutic study of 26 patients whose neurological disorders were characterized by spasticity, rigidity, and various dyskinesias and in 32 patients with one or more types of seizures.

The only clinical feature benefited in 13 patients with paralysis agitans was the oculogyric phenomenon in 2 of the 4 patients with this symptom. One of the seven patients with pyramidal system disease experienced some lessening of the severity of flexion spasms at night, which may have been apparent because of a sedative effect; and two of these patients felt some subjective improvement of mood. There was no benefit in two patients with cerebellar manifestations or in four patients with hyperkinetic disturbances. In the seizure-free groups toxic symptoms of drowsiness followed by unsteadiness and slowing of thought were produced by doses ranging from 2.4 to 6.8 gm. a day.

The frequency was decreased in 2 of the 21 patients having generalized convulsions. Psychomotor seizures were decreased in 1 of 11 patients. One of the three patients with focal seizures was somewhat improved. The frequency of seizures was less in two of the eight patients having petit mal seizures. Forty-one per cent experienced bothersome side-effects while taking from 1 to 4 tablets of meprobamate daily, and three reported an increase in seizures. All of the patients apparently benefited by meprobamate were better controlled by other drugs.

On the basis of the results obtained in this study, it is concluded that meprobamate is of little or no value in the treatment of neurological disorders characterized by spasticity, rigidity, dyskinesias, and convulsive states.

Discussion

Dr. Nathan S. Schlezinger: The silence of the audience is somewhat difficult to understand. The literature of our daily mail is deluding. Our studies tend to show that if there is any benefit in this drug it lies in fields other than neurological disorders. We have been impressed with the relatively low toxicity of this drug.

Impairment of Recent Memory Due to Unilateral Temporal Lobe Lesions. Dr. A. Earl Walker.

Four cases of temporal lobectomy are presented to illustrate the type of memory defect which may occasionally follow such lesions. Briefly, the mental changes resulting from some anterior temporal lobectomies have the following characteristics:

1. Superimposed upon a relatively intact intelligence, as measured by the formal I. Q., and a normal personality is a loss of memory for recent events with preservation of the ability to remember remote happenings. This may be so slight that the patient has no difficulty in carrying out his usual activities, or it may be so devastating that the patient cannot follow a drama or plot on television or radio.

2. Immediate recall is usually intact, for patients may be able to repeat nonsense syllables or series of numbers unless a minor diversion of attention is interposed between the giving of the test data and its repetition.

3. The memory impairment does not seem to affect the aquisition or retention of motor skills.

The anatomical basis would seem to be local cortical, possibly hippocampal, damage rather than interruption of afferent or efferent tracts from the medial temporal structures.

Discussion

DR. G. M. AUSTIN: This is an interesting paper and an important set of observations. I am interested in several findings which make me wonder about the mechanisms. In three of the patients the memory deficit was gradually cumulative. In one the memory deficit was rapid. An acute memory deficit occurred in the aneurysm case. Were there any changes in the EEG over a period of months which might indicate that some psychomotor seizure mechanisms might still remain, and possibly block out memory patterns by a process of occlusion? EEG tracings might throw some light on this. In cases of gradual impairment, one must think of residual scarring with gradual vascular occlusion by scars. Does Dr. Walker have any ideas about new psychological tests which might be more sensitive indications of memory loss?

DR. MICHAEL SCOTT: This is a stimulating paper. Does Dr. Walker have similar observations in patients having small temporal lobe tumors?

DR. ALEXANDER SILVERSTEIN: I should like to ask Dr. Walker, in view of his experiences with the serious complication of memory deficit in his group of patients with temporal lobectomies, whether he would hesitate to perform this operation in the future. Is there any way of predicting prior to operation in which type of case this complication might develop?

DR. RICHARD G. BERRY: Is there any evidence that the vascular supply might have been compromised in the older age group? Could such added factors as vascular damage or the results of impaired circulation account for the memory deficits?

DR. WILLIAM H. WHITELEY: Has Dr. Walker had any experience with bilateral temporal lobectomies?

DR. DAVID J. LAFIA: Did the material removed throw any light on the cause for the memory deficit?

DR. NATHAN S. SCHLEZINGER: We need more material from which to draw any conclusions. We know Dr. Walker's syndrome as presented as the organic mental syndrome. In what way does his syndrome differ from that seen in other organic brain processes?

DR. A. EARL WALKER: Three of the patients noted the memory deficit immediately after operation, and all tended to improve. In the second case the patient improved so that she was able to carry on in a responsible business position. I think this improvement rules out residual scarring and vascular pathology as causes of the amnesia. EEG tracings after surgery have been normal or have shown improvement over the preoperative records. The literature of tumors makes little mention of memory impairment, but it does occur in 15% of tumor or lobectomy cases.

This complication is not serious enough to contraindicate temporal lobectomy for psychomotor seizures. The memory deficit differs from that seen in the organic mental syndrome in that recent memory only is affected; other aspects of behavior and personality remain normal. It is impossible to rule out the possibility of interference with the blood supply of the posterior hippocampus. The visual fields are normal except for a small nick in the upper temporal quadrant.

Value of Hypothermia in Treatment of Aneurysms of the Circle of Willis. DR. G. M. AUSTIN, DR. ANN SAYEN (by invitation), DR. GRAYSON P. MCCOUCH, and DR. FRANCIS C. GRANT.

We have now used hypothermia in the direct surgical approach for eight successive aneurysms of the circle of Willis. The operative mortality was 12.5%, one patient dying of thrombosis of the circle of Willis on the 30th postoperative day. Although the position of the aneurysms varied and not all required carotid-vertebral occlusion during hypothermia, in two of the cases there was severe hemorrhage, which could be controlled only by means of complete vascular occlusion. Complications have consisted mainly of postoperative carotid thrombosis in cases in which the common carotid was occluded in the neck before hypothermia. Apparently, sludging tends to develop with hypothermia, followed by postoperative thromboses. This occurred in three of our patients. Since the hemiparesis was not present preoperatively, and since in two patients there was no carotid-vertebral occlusion during surgery, a prolonged drop in blood pressure may be an important factor.

Our polarographic studies of brain oxygen availability in monkeys shows a wide range of response to carotid occlusion. Although hypothermia seems to afford some protection to carotid occlusion, the increased oxygen availability under hypothermia, together with carotid occlusion, is probably due to lowered metabolism plus adequate vertebral circulation through the posterior communicating artery.

Discussion

DR. GRAYSON P. MCCOUCH: It is an act of generosity to include me in the paper. I was merely cheering from the side-lines. I would like to ask one question: Is it safe to do hypothermia in patients whose metabolism is low?

DR. RICHARD G. BERRY: Do the authors have any explanation for the paradoxical reaction noted in one case? Were any anatomical studies done on the circle of Willis?

DR. ALEXANDER SILVERSTEIN: I enjoyed listening to this interesting paper by Dr. Austin and would like to hear more about the complications of this form of anesthesia. Recently, on my service at the Philadelphia General Hospital, a patient with an unruptured aneurysm who was prepared for surgery by this form of anesthesia died as a result of hypothermia. It would seem to me that careful observation and great care are necessary for the administration of this type of anesthesia.

DR. HENRY A. SHENKIN: The results you present of occlusion of a carotid vessel in the monkey do not appear to be very consistent. In any event, it would appear that your criteria for protection of the cerebral metabolism during hypothermia is determined solely by oxygen availability. Is it so clear that if there is an increased "oxygen availability" with hypothermia following occlusion of a carotid vessel it can be inferred that the hypothermia will protect the metabolic function of the brain?

DR. A. EARL WALKER: I must congratulate the authors; we need more investigations of this type, but I wonder whether the first monkey was not an aberrant one? Usually we can tie off both carotids and one vertebral artery without impairment of intracranial blood supply. I notice there was a great drop in blood pressure in the first monkey after carotid occlusion. Did the animal have insufficient development of the basilar system? In the last three monkeys the findings ran true to form. Apropos of hypothermia in intracranial aneurysm, we must learn more about this technique. I wonder whether after 100 cases of hypothermia, the results would be better than with previous methods?

I would like to suggest that in reporting results the site of aneurysms be given. We know that mortality rates depend on the site. For example, there is a high mortality in basilar artery aneurysms. Moreover, statistics of aneurysm surgery are meaningless unless we know the time interval between rupture and surgical attack, for the prognosis improves if the patient survives for a certain time.

DR. G. M. AUSTIN: I realize that there is a definite risk in this method. I should like to stress the help obtained by us from the anesthetist. We pay particular attention to the cardiovascular system when the temperature is lowered. During the procedure we monitor the patient with the EKG. The age of the patient is important, since we do not use this method in patients past the age of 55. We get a complete medical clearance before the operation. We lost one patient prior to operation while she was undergoing hypothermia. At autopsy we found that she had had a coronary stenosis. In answer to the question of how long we occluded the vessels: It was two minutes each in the monkeys. In the human cases, the time varied from one and one-half to four and one-half minutes. All of our patients are operated upon within the first few weeks following the original rupture. On the basis of our theory, the optimum time for operation is from the 7th to the 10th day.

Abstracts from Current Literature

Edited by Dr. Bernard J. Alpers

Anatomy and Embryology

The Thalamus of Anthropoids. Kaspar Simma, Psychiat. et. neurol. 134:145 (Sept.-Oct.) 1957.

Simma supplements the anatomy of the primate thalamus by comparing the cellular structures of monkeys, chimpanzee, and man (all three having already been investigated to some extent) with those of two anthropoid apes, the orangutan and the gorilla. The method used is that of examination of coronal Nissl preparations utilizing sections cited in previous studies. The gross general cellular picture is identical for all forms, insofar as both the specific nuclei and their topographic relationships are concerned. Relative variations are encountered, among which are predominance of the dorsomedial nucleus, pulvinar, certain lateral nuclear complexes, and the parafascicular nuclei in man, with less prominence in apes and still more minor status in rhesus monkeys. The centrum medianum is also larger in man and apes than in monkeys. On the other hand, the intralaminar nuclei and habenula are more highly developed in monkeys than in apes and man. Qualitatively, one notes a greater tendency toward predominance of a single type of cells with encroachment of scattered "foreign" cellular elements in higher apes, while a more rigid arrangement, with two cell types predominating, obtains in man.

Parsons, Montrose, N. Y.

Physiology and Biochemistry

Effects of l-Arginine on Hepatic Encephalopathy. J. L. Fazekas, H. E. Ticktin, and J. G. Shea, Am. J. M. Sc. 234:462 (Oct.) 1957.

Ten patients with hepatic insufficiency and associated cerebral dysfunction were studied to ascertain the effects of the infusion of 25 to 37 gm. of l-arginine over a one- to three-hour period. Measurements were made of cerebral blood flow, cerebral oxygen utilization, arterial blood ammonia, and blood urea nitrogen. There was a reduction in the arterial blood ammonia for three hours after the infusion but no change in cerebral oxygen consumption. Of the 10 subjects, 5 improved sufficiently to be discharged from the hospital, although there was no sustained alteration of blood ammonia levels. The immediate reduction of blood ammonia levels was in itself not correlated with any change in cerebral function.

Berlin, New York.

Seizures with Promazine. J. F. Kurtzke, J. Nerv. & Ment. Dis. 125:119, 1957.

Promazine was given in initial doses of 75 to 300 mg. a day and in maintenance doses of 900 to 1800 mg. a day to 21 chronic psychotic patients. In a two-month period, six patients had 11 grand mal seizures. The incidence of seizures dropped strikingly after discontinuing this drug. Among the five subjects who had had EEG records before treatment, it was observed that two had developed abnormal EEG patterns after treatment with promazine had been instituted during this study.

Berlin, New York.

Recording and Stimulation of the Rhinencephalon with Implanted Electrodes in Man. A. E. Walker and M. Ribstein, Rev. neurol. 96:453 (June) 1957.

Copper electrodes were inserted in the amygdala and hippocampus of four patients and kept there for four weeks. Stimulation was by a thyratron stimulator providing 3-5-volt saw-toothed waves at 60 cps for five seconds. It was found that the amygdala has 9-cps waves, not influenced by sensory stimuli and slowed by sleep. Stimulation of the amygdala induced a loss of consciousness for 40 seconds, followed by amnesia, and associated with high-voltage spike-waves limited to one amygdala. Scalp electrodes did not invariably show these discharges. In the hippocampus there were single or groups of high-voltage spikes superimposed on the normal rhythm, their frequency ranging from 6-8 to 15 cps. There

was a very low threshold for inducing seizures from the hippocampus, and the accompanying electrical activity consisted of a volley of spikes, followed by spike-waves and then slow waves.

BERLIN, New York.

Neuropathology

NEUROBLASTOMA AND RELATED TUMORS. D. STOWENS, A. M. A. Arch. Path. 63:451 (May) 1957.

Stowens has reviewed the clinical and pathologic data from 236 tumors of the sympathetic nervous system seen at the Armed Forces Institute of Pathology. There were 110 neuroblastomas, 109 ganglioneuromas, and 17 ganglioneuroblastomas. Of the neuroblastomas, 39 were primary in the adrenal gland, 37 were retroperitoneal, 12 were mediastinal, and 12 were located in other sites. Most of these tumors were unencapsulated and frequently disclosed areas of hemorrhage and necrosis. Microscopically, rosettes were seen in 15% of the group. Forty-eight neuroblastomas occurred during the first year of life, and only twenty-three were seen after the age of 14. All the 14 patients with neuroblastoma (13% of the total with follow-up) who survived 18 months or more after surgical removal of the tumor were less than 4 years of age. The average survival of patients with neuroblastoma older than 4 years was 11 months. In 8 of the 14 survivors the tumor was retroperitoneal and arose between and close to the adrenal gland and kidney but did not involve either organ; 10 of these neoplasms were encapsulated. Metastases occurred to many organs but involved chiefly bones, regional lymph nodes, liver, and lungs. Although the adrenal gland was the primary site in 51% of neuroblastomas arising before the fourth year, the incidence was only 13% in the adult group. The author, therefore, believes that this lesion encompasses two forms: a congenital tumor resulting from disruption of normal embryogenesis of the sympathetic nervous system, amenable to surgical therapy in one-third of the cases and capable of undergoing spontaneous regression, and an invariably fatal neoplasm, the product of malignant degeneration of fully mature sympathetic nerve tissue.

The ganglioneuromas were always encapsulated, and 23% were grossly calcified. They, of course, did not metastasize. Death was attributable to the tumor in only one patient, in whom the tumor invaded the base of the skull. No ganglioneuromas were seen before the first year of life, and only 11 occurred before the age of 14. Of these tumors, 30 were primary in the adrenal gland, 18 were retroperitoneal, 38 were mediastinal, and 14 occurred in other sites.

Eleven ganglioneuroblastomas involved the retroperitoneal space; two were found in the adrenal gland; two in the mediastinum, and two in the neck. Eleven such tumors occurred before the 14th year of life. Considerable variation was encountered in the patterns of combination of neuroblastoma and ganglioneuroma. It was not possible to correlate microscopic appearance with clinical course. The predominating cells often resembled a mature ganglion cell but possessed greater density of chromatin material, eccentricity of the nucleus, and scantier cytoplasm. Eight patients (31% of those with follow-up) were alive 18 months later without evidence of recurrence of the tumor or of metastases. The clinical course was invariably more prolonged than in the neuroblastoma group, although the sites of metastases were similar. Because of variations in anatomical location, clinical behavior, and age groups involved, the author believes that neuroblastoma and ganglioneuroblastoma are essentially distinct diseases of the same system, rather than different manifestations of the same disease.

APONTE (MC), U. S. N. R.

GLIOMATOSIS CEREBRI. J. DUNN JR. and J. W. KERNOHAN, A. M. A. Arch. Path. 64:82 (July) 1957.

Two cases of diffuse cerebral gliomatosis are described. In the first one, an 18-year-old woman, the brain disclosed diffuse enlargement of the right cerebral hemisphere with flattening of the convolutions. The corpus callosum was thickened. Neoplastic glial elements were seen throughout the cerebral hemispheres and brain stem. Involvement was consistently greater in the white matter than in the cortex. Invasion of the mesencephalon, pons, and medulla was confined to collections of tumor cells in relation to long-fiber tracts and could not be tracted below the upper medullary level. Cerebellar involvement was limited to the central nuclear masses. Demyelination and degeneration of neurofibrils occurred secondary and in direct proportion to the severity of neoplastic invasion. The astrocytic nature of the tumor

cells was confirmed by use of Cajal's gold-sublimate and Hortega's triple impregnation staining techniques. The typical cell was elongated and appeared as a polar spongioblast. In the gray matter the more typical astrocytic forms predominated. Protoplasmic astrocytes were occasionally seen in small zones of necrosis. Cellularity was greatest in the corpus callosum, basal ganglia, internal capsule, frontal areas and parieto-occipital lobes. Where cellularity was greatest, there were seen subpial collections of neoplastic cells. Cortical involvement was most pronounced in these areas of pial extension. Marked pleomorphism was observed. Bizarre and multinucleated forms, resembling those seen in glioblastoma multiforme, were present, and abnormal mitoses were common. In the brain of the second case, a woman aged 20, there were edema, flattening of the cortical convolutions, thickening of the corpus callosum and fornix bilaterally, and enlargement of the head of the caudate nucleus on the right. Microscopically, the lesion was qualitatively similar to that in the first case. There was, however, a greater degree of edema and of neoplastic invasion of the cortex. Protoplasmic astrocytes were oftener found in the white matter than in the first case. Extension of glial tissue into the leptomeninges at the cortical levels was also more intense. The corpus callosum was severely involved. Sporadic tumor cells were present in the pons, mesencephalon, and central nuclear masses of the cerebellum. The medulla and cerebellar hemispheres were spared.

The various theories of histogenesis of this interesting lesion are briefly reviewed. The authors consider the absence of immature neuronal elements in their cases as evidence against the hypothesis of origin from embryonic rests. A derivation of the tumor from Schwann cells they consider highly improbable. The extensive neoplastic spread, they state, argues strongly in favor of a multicentric origin. The authors view the entity of cerebral gliomatosis as true neoplastic transformation of the malignant astrocytoma type.

APONTE (MC), U. S. N. R.

MARFAN'S SYNDROME WITH UNUSUAL BLOOD VESSEL MANIFESTATIONS. M. G. AUSTIN and R. F. SCHAEFER, A. M. A. Arch. Path. 64:205 (Aug.) 1957.

Austin and Schaefer describe the necropsy findings in a white man aged 25 who died as a result of a dissecting aneurysm of the innominate and right common carotid arteries. There was extensive malacia of the right cerebral hemisphere. Although a family history of the disease could not be obtained and there was no subluxation of the lenses, the case fulfills many of the criteria of Marfan's syndrome. Clinically, there were long extremities, hyperelasticity of the skin, hypermobility of the joints, a highly arched palate, kyphoscoliosis, marked bilateral keratoconus, slight cardiomegaly, and an apical systolic cardiac murmur. Autopsy showed that the mitral orifice was dilated and the mitral leaflets thick and redundant. Hemorrhage had dissected through the wall of the innominate artery, partially occluding it, and had extended into the right common carotid, completely obliterating the lumen of that vessel. The common carotid artery in the left was narrowed by a circumscribed area of dissection 2.0 cm. long. The aorta was not involved by the dissecting aneurysm. Microscopically, the changes of cystic medionecrosis were observed in the media and intima of the aorta and right common carotid artery. These contained multiple cystic spaces filled with a faintly basophilic, Schiff-positive material. The elastic fibers in and around the small cysts were fragmented. The findings in the brain are not described in detail; the lateral ventricles were compressed by the edematous cerebral tissue.

APONTE (MC), U. S. N. R.

LEPTOMENINGITIS DUE TO SPOROTRICHUM SCHENCKII. E. H. SHOEMAKER, H. D. BENNETT, W. S. FIELDS, F. C. WHITCOMB, and B. HALPERT, A. M. A. Arch. Path. 64:222 (Aug.) 1957.

Shoemaker and associates report the second case of leptomeningitis due to Sporotrichum schenckii diagnosed during life. Whereas in the other reported case cutaneous lesions were also present, in the present one only the central nervous system was involved. Clinical manifestations had become apparent at least two months prior to admission to the hospital and consisted of headaches, dizziness, loss of memory, mental deterioration, olfactory hallucinations, and ataxia. Roentgenograms of the skull and a left carotid angiogram were normal. Pneumoencephalograms revealed symmetrical dilatation of the lateral and third ventricles but not of the fourth. Electroencephalograms were repeatedly abnormal. The fungus was cultivated from cerebrospinal fluid. A positive skin test was elicited employing a 1:1000 dilution of an extract from the mycelial phase of the organism. The results of multiple

lumbar punctures are outlined. There was a consistent lymphocytic pleocytosis with elevated concentration of protein, but the pressure was normal. At autopsy the abnormal gross findings in the brain consisted of thickening of the leptomeninges at the base and generalized hyperemia. Microscopically, collections of lymphocytes, plasma cells, and histiocytes were seen in the leptomeninges of the cervical cord and in some of the Virchow-Robin spaces of the medulla. In the leptomeninges at the base of the brain were observed prominent granulomas, consisting of large areas of necrosis, surrounded in palisade fashion by epitheloid cells and containing neutrophils and nuclear debris. The organism was not seen in the routine preparations stained with hematoxylin and eosin but could be identified in sections stained by the Gridley and periodic acid-Schiff methods.

APONTE (MC), U. S. N. R.

EXTRACRANIAL METASTASIS IN A CASE OF INTRACRANIAL EPENDYMOMA. R. E. PERRY JR., A. M. A. Arch. Path. 64:337 (Sept.) 1957.

The patient, a man aged 39, had undergone craniotomies for a tumor of the left parietal lobe six years and one year prior to death. After the second craniotomy roentgen ray therapy had been administered. At necropsy a firm white nodule of tumor, measuring 3.5×2.5×3.0 cm., was found in the left superior parietal lobule. It extended downward from the vertex for a distance of 2 cm. into the precuneus. A mass of soft tumor involved the meninges of the spinal cord 22 cm. below the medulla oblongata and compressed the cord at that level. Metastatic implants were also seen in the liver and femoral bone marrow. The lesion, in both surgical and autopsy material, consisted of compact sheets of small cells with regular dark nuclei. In the tissue obtained post mortem, material staining positively with the mucicarmine and periodic acid-Schiff methods was identified within their cytoplasm. A few pseudorosettes were seen. Production of glial fibers by the tumor cells was not demonstrated when the tissue was stained with phosphotungstic-acid hematoxylin, but reactive gliosis around the neoplasm was common. Nodules of tumor were also found in the wall of the left ventricle and in the pituitary stalk. The morphology of the lesion in the leptomeninges of the thoracic cord, liver, and femoral bone marrow was basically similar to that in the brain. No evidence was found of degeneration of the spinal tracts at the site of compression. This is the fourth reported case of an ependymoma of the central nervous system with remote metastases. One of these was primary in the spinal cord, and in another, which had metastasized to the cervical lymph nodes, autopsy was not performed. All four cases have had in common (1) prolonged survival (2½ to 13 years), (2) multiple craniotomies (two to four), and (3) postoperative irradiation.

APONTE (MC), U. S. N. R.

EXPERIMENTAL CEREBRAL INFARCTION: THE EFFECT OF DICUMAROL. W. S. SIBLEY, J. H. MORLEDGE, and L. W. LAPHAM, Am. J. M. Sc. 234:663 (Dec.) 1957.

In order to evaluate the effects of anticoagulant drugs on experimentally produced encephalomalacia, homologous clot fragments were injected into the carotid arteries of dogs. Two groups of dogs, each with neurological deficits induced in this way, were studied. One group was given 10 mg/kg. of bishydroxycoumarin U. S. P. (Dicumarol). Usually bishydroxycoumarin was given 24 hours prior to surgery, but in several instances the drug was administered for the first time one to four days after cerebral infarction. Clinical and pathological examinations revealed that the sizes of the infarcts produced were comparable in the control and in the bishydroxycoumarin-treated group. Six deaths occurred in less than 24 hours after infarction, and there was no apparent difference in the sizes of the lesions of the treated and of the untreated group. Among the animals that improved, none showed worsening of symptoms once improvement started. Of the 12 animals treated with bishydroxycoumarin and surviving the acute phase of infarction, 4 animals subsequently died as a result of hemorrhagic changes occurring in or about the area of infarction. Five of the seven animals treated with bishydroxycoumarin and surviving had anemic infarcts. It was concluded that bishydroxycoumarin increased the hemorrhagic tendencies of experimentally produced embolic infarcts in dogs.

BERLIN, New York.

HYPERERGIC ENCEPHALOMYELITIDES FOLLOWING EXANTHEMATIC DISEASES, INFECTIOUS DISEASES AND VACCINATION. A. FERRARO and L. ROIZIN, J. Neuropath. & Exper. Neurol. 16:423 (Oct.) 1957.

In a condensed presentation, most adequately illustrated, the authors report close similarity between, if not identity with, the pathology of postexanthematic, postinfectious, and post-

vaccinal and acute hemorrhagic encephalitis in humans and the pathology of experimental allergy and cerebral anaphylaxis in animals. On the basis of wide experience in the pathology of animal experimentation and its relation to human material, the authors advocate the theory, originally presented by Glanzmann and van Bogaert, that these encephalomyelitides are the result of an immunologic-allergic reaction of the central nervous system to antigenic stimuli.

They propose the term hyperergic postinfectious or postvaccinal encephalomyelitis to cover the various categories and implement their belief of the allergic etiology with the following factors: (1) the existence of a constitutional predisposition, (2) the possibility of previous exanthemic or infectious disease producing a susceptibility of the central nervous system to allergic reactions, and (3) the possibility that a viral or bacterial infection or toxins may trigger off the allergic reaction.

AIGNER, Rochester, Minn.

BILATERAL SYMMETRICAL DEGENERATION OF THE THALAMUS. S. SCHULMAN, J. Neuropath. & Exper. Neurol. 16:446 (Oct.) 1957.

Schulman reports in detail the case of a 50-year-old white man who died in coma after an illness of approximately six months. The original symptoms, and the only ones for the first three months, were those of progressive mental deterioration. After the third month there was the gradual onset of increasing generalized ataxia, somewhat more marked on the right; a "tight feeling" on the right side of his face, and numbness of the right arm and leg, which spread after a month to involve the left side. The patient entered the hospital about five months after the onset of his difficulties. Examination revealed intellectual deterioration, affective disturbances, and bizarre general behavior. Calculation was poor. Lack of insight into his condition was evident. The reflexes were normal, and the plantar responses were flexor. Sensory examination was apparently normal. Two weeks after hospitalization he developed generalized choreoathetoid movements of the face and limbs. Later occasional single myoclonic jerks were interspersed among the choreiform movements, and long periods of shifting clonic convulsions were observed, occasionally generalized. Later his behavior became more bizarre, with emotional outbursts, and two weeks before death he lapsed into coma.

The only abnormal laboratory findings were the electroencephalogram, which revealed generalized slow activity of 3-6-per-second frequency and high amplitude, and pleocytosis and elevated spinal fluid protein, thought to be secondary to iophendylate (Pantopaque) myelography seven weeks before death.

Autopsy revealed the primary pathology to be in both thalami. Here extensive symmetrically bilateral degeneration was found, associated with moderate astrocytic gliosis. The blood vessels in the thalami were normal, and no evidence of necrosis or inflammation was found. The degeneration was limited to certain nuclear groups, and others were entirely preserved. The severest degeneration was found in the medial and lateral nuclei and in the pulvinar. The intralaminar and midline nuclei and the lateral and medial geniculate bodies were not involved.

AIGNER, Rochester, Minn.

DECORTICATION AS A RESULT OF WIDESPREAD CIRCULATORY AND ANOXIC DAMAGE. W. ZEMAN and E. YOUNGUE, J. Neuropath. & Exper. Neurol. 16:492 (Oct.) 1957.

The authors present the case of a 32-year-old Negro soldier who was an alcoholic and ex-boxer. After the acute onset of unexplained repeated grand mal convulsive episodes complicated by shock and asphyxia, the patient lapsed into a persistent semistuporous condition, which persisted for 17 months, until his death. During this time he developed signs of decerebrate rigidity. The electroencephalographic tracing was isoelectric. He exhibited during the last six months inability to maintain body temperature, cessation of leukocytic response to widespread infection, and a peculiar day-night rhythm of response.

The morphologic examination of the central nervous system revealed symmetrical old ischemic lesions in the gray matter of the cerebrum and, partially, in the cerebellum, as well as Wallerian degeneration of the cortifugal pathways. The topography of the lesions was not that seen usually after hypoxic anoxia, and there was a marked discrepancy between the degree of Wallerian degeneration found below the midbrain and the slighter degree found above the peduncles.

AIGNER, Rochester, Minn.

BOECK'S SARCOID IN CHRONIC MENINGO-ENCEPHALITIS: ORGANIC PSYCHOSIS WITH MASSIVE SOFTENING DUE TO BOECK'S DISEASE. R. M. CARES, B. S. GORDON, and E. KREUGER, J. Neuropath. & Exper. Neurol. 16:544 (Oct.) 1957.

The authors report a case of meningoencephalitic sarcoidosis of four years' duration. The patient was a 34-year-old male Negro who complained initially of bilateral gradual loss of vision. This was followed after two years by headaches and progressive mental deterioration, manifested by mental slowness, failing memory, confusion, inattention, and untidiness.

Neurologic examination revealed an anosmia, moderate ataxia in gait, and hyperreflexia. The chief laboratory findings included a spinal fluid protein of 860 mg. % and a positive Kveim test. A craniotomy was performed, and compression atrophy of the optic nerves by pial adhesions was noted. Biopsy of the leptomeninges revealed tuberculoid granulomata histologically compatible with Boeck's sarcoidosis. Antituberculous therapy was of no avail.

Mental deterioration progressed with no marked neurologic development, and in the final year an organic psychosis supervened.

Gross and microscopic tissue studies revealed sarcoidosis of the cerebral white matter becoming progressively severer from the parietal and temporal to the occipital lobes. The frontal and anterior parietal areas were uninvolved. The widespread sarcoidosis caused demyelination, frequently leaving only the U-fibers intact and grossly resembling Schilder's disease. The cortex was uninvolved. The process heavily infiltrated the basal meninges, and scattered lesions were found over the cerebellum and brain stem.

Although the mediastinal lymph nodes presented some sarcoid tubercles, there was no evidence of sarcoid lesions in other nodes or organs of the body.

AIGNER, Rochester, Minn.

News and Comment

SOCIETY NEWS

Association for Research in Nervous and Mental Disease, Inc.—The Annual Meeting of the Association for Research in Nervous and Mental Disease will be held on Dec. 12 and 13, 1958, at the Hotel Roosevelt, New York. The subject of the meeting will be Neuromuscular Disorders.

A Combined Biochemical and Clinical Study of Mental Disease

I. Cholesterol Levels in Patients Receiving Deep Insulin Coma Therapy

WILLIAM H. HARRIS, B.S., and EARL S. PATTERSON, M.D., Middletown, Conn.

Introduction

Recent investigations in this laboratory of the ratio of cerebrospinal fluid calcium and magnesium in psychotic and nonpsychotic patients gave results which could be explained by the alteration of the permeability of the blood-brain barrier.[1,2] It was suggested that endocrine and other organ systems external to the central nervous system may have an effect on this permeability. Therefore it was decided to evaluate as many of these systems as possible in mental disease.

Because of the widespread use of ataractic drugs in mental hospitals, it is difficult to obtain a patient group whose metabolic processes may not have been altered. However, patients undergoing insulin shock therapy are drug-free and receiving no therapy except insulin. In addition, they have the same diet and approximately the same amount of exercise and recreation as well as excellent surroundings and attention. Furthermore, it has been shown at this hospital that insulin therapy has a pronounced beneficial effect on the patients treated.[3] Continuous biochemical and clinical studies on these patients from before the beginning of insulin shock therapy through to the end of the treatment could yield valuable information on the endocrine and other organ systems which might correlate physiological change with clinically observed recovery or failure. For these reasons, it was decided to perform the initial investigations on this group.

It has been observed in this laboratory for many years that the ratios of free to total serum cholesterol (F/T) and esterified to total serum cholesterol (E/T) are often inverted in acute psychotic episodes.

This effect has also been observed by Randall and Jellinek in their studies on insulin treatment of acute schizophrenics.[4] Our cases have been characterized by an increase or a decrease in the levels of free and esterified cholesterol such that the free cholesterol tends to become equal to or greater than the level of esterified cholesterol. While there is no definite relation between diseases of the liver and blood cholesterol,[5] it has been shown that the liver is principally responsible for the maintenance of free and esterified plasma cholesterol levels and the synthesis and destruction of this molecule.[6-8] It would be interesting to follow the variations of these fractions before and during insulin shock therapy. The results might be an index of the involvement of the liver in mental disease.

Submitted for publication Jan. 16, 1958.

From the Department of Biochemical Research and the Insulin Unit, Connecticut State Hospital.

Procedure

Clinical.—The patients studied in the present investigation are all from the Insulin Unit, which handles 20 patients at one time. They stay on this unit 24 hours a day during the treatment week, which lasts from Monday through Friday. The course of treatment averages 16 to 20 weeks. On Saturday and Sunday no therapy is given, and most of the patients leave the hospital on weekend visits. There is a high personnel-patient ratio, necessitated by the deep coma therapy and by the close clinical supervision exercised on the unit. Patients are rated periodically by all personnel during the testing period, using a simple 20-point questionnaire. In addition, patients are checked on a more complicated rating scale by the physician. This scale covers the use of symbols and mental activities; the patient's perceptual mechanisms, whether they yield to reality testing (hallucinations, hypnogogic experiences); affective life and activity, whether abnormally high or low and how related to reality; their demands, whether realistic or not, and their social behavior. Patients are rated 1 to 5, the higher number indicating the more psychotic type of behavior. The scores under these headings are totaled to provide a rough numerical idea of the clinical progress of the patients.

Patients were evaluated for discharge in the following manner: Those who have no signs of psychosis and are able to return to their previous social and occupational level are considered in remission. Those who have minor signs, such as slight flattening of affect, irritability, and moderate increase of physical activity, and who are able to return to their previous level of social and occupational life are considered much improved. These two classes are discharged from the hospital. The third category comprises patients who are able to maintain themselves with support outside the hospital but who have some minor signs of psychosis remaining and who are unable to return to their previous social and occupational level. These are considered improved but are not discharged. The fourth class of patients are those who have major psychotic symptoms remaining and are unable to return to previous levels. These patients are considered unimproved and are transferred to other sections of the hospital following treatment.

Biochemical.—Blood specimens were drawn from a total of 27 patients in the Insulin Unit at three different times. The first specimens were drawn on Monday from July 15 through Aug. 5 at 7:00 a. m., before the beginning of the weekly insulin treatment. The patients had had no treatment since the previous Friday, had been out of the hospital on their weekly visits, and were fasting. The second set of specimens were drawn on Monday, Oct. 21, when the conditions were the same as those described above, and on the following Thursday, the fourth day of insulin coma treatment. The third set were drawn on Thursday, Nov. 14, the fourth day of weekly insulin treatment, and then on the following Monday, Nov. 21, when conditions were the same as in the first collection, and the final specimens were drawn four days later, during the treatment week, on Thursday, Nov. 24. Blood specimens were obtained by venipuncture from the right or left antecubital space and cooled in a refrigerator at 10 C for about one hour. After centrifugation the sera obtained were analyzed for total cholesterol and cholesterol fractions by a modification of the method of Bloor and Knudson.[8]

Results

On July 15, when this experiment was begun, most of the patients, who were carefully selected and classified as schizophrenic, showed a marked disturbance of the cholesterol metabolism. The esters were very low, and the free fraction was often elevated above the ester level (inversion effect) (Table 1).

However, on the following Mondays (July 22 to Aug. 5) there was a general increase in total cholesterol, with a general rise in the E/T ratio toward the range of 0.60-0.70, and a disappearance of the inversion effect (Table 1). Out of this group five patients were able to be discharged three weeks later.

The experiments of Oct. 21 and 24 show that cholesterol ester levels are markedly decreased and free cholesterol levels often increased by insulin coma therapy (Table 2). The results, presented on Nov. 14, 18, and 21, confirm the effect of insulin on the cholesterol metabolism (Table 2). It is also observed that there is general increase in the E/T ratio during the entire testing period (Fig. 1). This increase correlates very well with the clinical course and discharge rate of the group (Table 2 and Fig. 2).

Comment

The work of Sperry, and later Bodansky, has established the very narrow range of

TABLE 1.—*Serum Cholesterol Levels Before Insulin*

Date *	July 15, 1957				July 22, 1957				July 29, 1957				Aug. 5, 1957			
	Serum Cholesterol				Serum Cholestero				Serum Cholesterol				Serum Cholesterol			
Patient No. †	Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %	Present Status
1	0.56	0.44	187	IE ‡	0.56	0.44	234	IE ‡	0.38	0.62	235	IE	0.39	0.61	278	Discharged 8/31/57
2	0.49	0.51	187		0.43	0.57	193		0.41	0.59	246					Discharged 8/31/57
3	0.46	0.54	180		0.48	0.52	225		0.38	0.62	235		0.33	0.67	261	
4	0.26	0.74	158		0.51	0.49	221	IE					0.38	0.62	295	
5					0.50	0.50	276		0.51	0.49	318	IE				
6	0.66	0.34	138	IE	0.79	0.21	209	IE					0.35	0.65	252	Discharged 8/31/57
7	0.24	0.76	300		0.43	0.57	290		0.39	0.61	346		0.33	0.67	330	Discharged 11/7/57
8	0.60	0.40	372	IE	0.45	0.55	262		0.41	0.59	336		0.26	0.74	278	
9	0.69	0.31	200	IE	0.47	0.53	206		0.23	0.77	230		0.35	0.65	261	Transferred
10	0.71	0.29	151	IE	0.53	0.47	248	IE	0.47	0.53	328					Transferred
11	0.73	0.27	276	IE	0.48	0.52	283		0.34	0.66	355		0.33	0.67	348	
12	0.55	0.45	194	IE	0.47	0.53	248		0.33	0.67	258		0.43	0.57	305	
13	0.65	0.35	180	IE	0.37	0.63	242		0.46	0.54	336		0.38	0.62	339	
14					0.44	0.56	207		0.49	0.51	282		0.39	0.61	287	Discharged 8/27/57
15	0.64	0.36	194	IE	0.56	0.44	173	IE	0.45	0.55	200		0.30	0.70	165	Discharged 8/31/57
Av.	0.56	0.44	201	IE	0.50	0.50	233		0.40	0.60	264		0.35	0.65	264	

* All dates represent Mondays at 7:00 a. m., after 12 hours fasting, before insulin, and after an insulin-free weekend.

† Patient numbers indicate the same patient in the two tables.

‡ IE stands for inversion effect.

TABLE 2.—*Serum Cholesterol Before and During Insulin Treatment*

Date *	Oct. 21, 1957				Oct. 24, 1957				Nov. 14, 1957				Nov. 18, 1957				Nov. 21, 1957				
	Serum Cholesterol				Serum Cholesterol				Serum Cholesterol				Serum Cholesterol				Serum Cholesterol				
Patient No.	Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Free %T	Esters %T	Total Mg. %		Present Status
3	0.40	0.60	311		0.57	0.43	294	IE	0.49	0.51	250		0.46	0.54	328		0.34	0.66	216		Discharged 12/18/57
4					0.43	0.57	221		0.40	0.60	256										Discharged 11/27/57
5	0.45	0.55	333		0.46	0.54	242		0.27	0.73	240		0.37	0.63	336		0.38	0.62	320		Continuing treatment
8	0.39	0.61	318		0.53	0.47	294	IE	0.39	0.61	272		0.25	0.75	288		0.31	0.69	264		Discharged; readmitted
11									0.27	0.73	287		0.34	0.66	400		0.29	0.71	376		Continuing treatment
12	0.22	0.88	370		0.38	0.62	390		0.46	0.54	368		0.26	0.74	432		0.29	0.71	336		Continuing treatment
13			415		0.37	0.63	336		0.46	0.54	250		0.30	0.70	296		0.25	0.75	248		Discharged 11/27/57
16	0.32	0.68	340				347		0.52	0.48	240	IE	0.37	0.62	312		0.43	0.57	224		Continuing treatment
17	0.51	0.49	229	IE	0.53	0.47	179	IE	0.43	0.57	280		0.41	0.59	312		0.37	0.63	264		Discharged 11/27/57
18	0.25	0.75	226		0.50	0.50	168		0.40	0.60	200		0.34	0.66	256		0.32	0.68	200		Continuing treatment
19	0.37	0.63	259		0.59	0.41	180	IE	0.44	0.56	200		0.32	0.68	272		0.53	0.47	216	IE	Continuing treatment
20	0.33	0.67	355		0.47	0.53	316		0.36	0.64	287		0.31	0.69	336		0.33	0.67	272		Continuing treatment
21					0.68	0.32	168	IE	0.48	0.52	216		0.29	0.71	248		0.41	0.59	232		Discharged 11/27/57
22	0.32	0.68	229		0.76	0.24	126	IE	0.90	0.10	200	IE	0.32	0.68	272		0.42	0.58	208		Discharged 11/27/57
23	0.50	0.50	281		0.64	0.36	232	IE	0.40	0.60	216		0.25	0.75	256						Continuing treatment
24	0.31	0.69	289		0.30	0.70	210		0.41	0.59	232		0.25	0.75	256		0.34	0.66	240		Continuing treatment
25									0.52	0.48	168	IE	0.30	0.70	216		0.45	0.55	152		Continuing treatment
26									0.50	0.50	240		0.36	0.74	272		0.35	0.65	296		Continuing treatment
27									0.61	0.39	287	IE	0.48	0.52	168		0.44	0.56	168		Continuing treatment
Av.	0.36	0.64	329		0.51	0.49	247	IE	0.46	0.54	246		0.33	0.67	292		0.37	0.63	254		

* Oct. 21 and Nov. 18 represent the same conditions as in Table 1; Oct. 24 follows four days of insulin treatment; Nov. 14, four days of insulin treatment at a later date; Nov. 21, four days of insulin treatment, beginning Nov. 18.

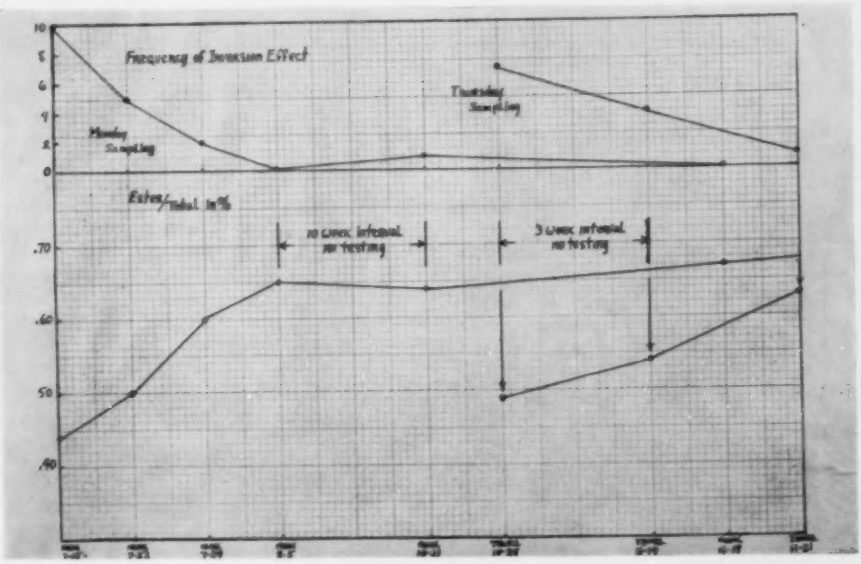

Figure 1

the normal ratio of free to total serum cholesterol (F/T) as 0.27-0.30 and of esters to total serum cholesterol (E/T) as 0.70-0.73.[10,11] The normal range of total serum cholesterol is 150-250 mg. %. Gildea and Man [12] and Schube [13] have shown that manic-depressive and schizophrenic states are accompanied by low serum cholesterol levels, which rise as the patient recovers. We have been unable to confirm these findings despite the fact that our total cholesterol values show a rise as the course of insulin therapy progresses, because nearly all our values lie within the normal range. However, we are in pretty good agreement with the findings of Randall and Jellinek,[4] who state that the cholesterol esters are low in acute schizophrenia before insulin shock therapy and that the free and esterified cholesterols are elevated after treatment if recovery has occurred. In our cases there is a consistent rise in the E/T ratio in bloods drawn on Monday throughout the entire series, but there is a parallel decrease in the F/T ratio. The important variation in our series is the rise or fall of the E/T ratio, for when the E/T ratio, over a course of insulin therapy, rises consistently toward the normal ratio level, there is generally evident good clinical improvement. There is much less correlation between clinical improvement and absolute values, in milligrams per cent, of cholesterol or its fraction (Tables 1 and 2). We have found that over 84% of the patients who improved to the discharge level displayed this concomitant rise in the E/T ratios. Of the patients showing little or no clinical improvement, only 33% showed this rise (Table 3). Patients showing stable values, values falling away from normal ratios, or values fluctuating but always returning to lower levels generally did not improve clinically and are still undergoing intensive therapy. Illustrative of the foregoing points are the following case histories.

Report of Cases

PATIENT 2.—A 33-year-old white man was admitted to the hospital on Oct. 26, 1956. Upon admission the patient showed symptoms of schizophrenic reaction, catatonic in type. He was withdrawn, delusional, and hallucinative, with psychomotor retardation and blocking. The patient felt that he was destined to be the last man on earth

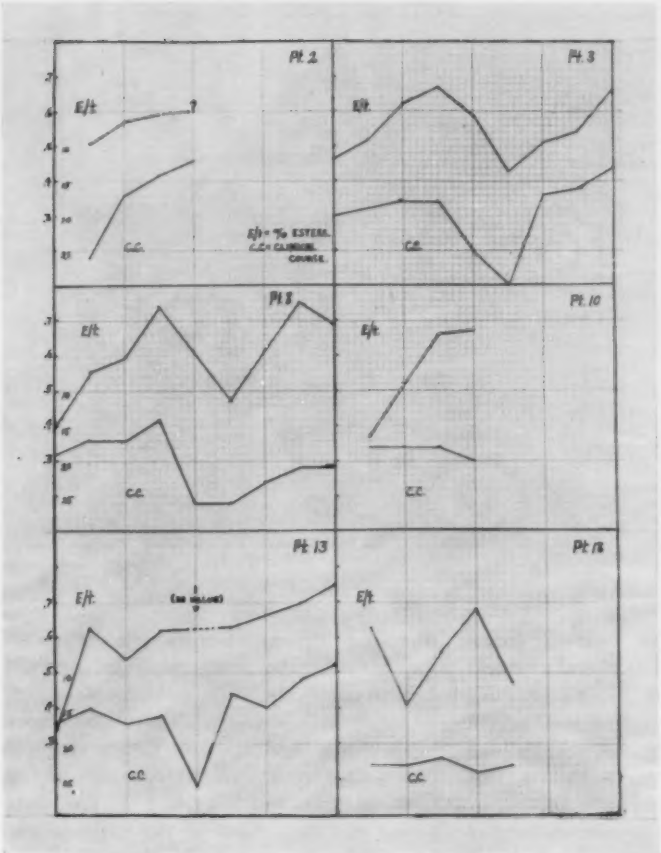

Figure 2

TABLE 3.—*Correlation of Clinical Improvement and Rise in E/T Ratios*

Level of Esters	Analysis of Patients Discharged: No. of Patients	%	%	Analysis of Patients Not Discharged: No. of Patients	%	%
Rise to 0.70	3	23.09		1	8.3	
Rise to 0.60-0.69	6	46.2		2	16.7	
Rise to 0.50-0.59	2	15.4		1	8.3	
Total No. increase toward normal	11		84.6	4		33.3
No. decreased from normal or with no change	2		15.4	8		66.6
Totals	13		100	12		100

and that he would have to make a rocket flight to the sun for some purpose which was obscure to him. All his activities seemed to relate to this rather shattering delusional system. He showed outbursts of violence, which apparently were acts of resentment over his imagined fate. He had continual deep burns on his hands and arms from the application of cigarettes and cigars. He burned himself in an effort to learn whether he could withstand the heat of the sun.

The patient's condition continued unchanged in February, 1957, when he was transferred to the Insulin Unit. He was at that time entered in a placebo experiment and received only injections of sterile water. His symptoms remained unabated until July, 1957.

During the week of July 15 to July 22, 1957, he showed a rather striking change. He became

able for the first time to verbalize his delusional system and began to feel it was a symptom of a mental illness. The violent outbursts began to abate, and he began to show some socialization on the ward. This improvement in his mental status continued, and within two more weeks the patient lost every major symptom of psychosis. He was verbalizing very well and was cooperative. He showed an affect that was appropriate and clearly related patterns of thought. He gained limited insight into his illness and was making realistic plans for his discharge. By Aug. 13 the patient was in complete remission and was discharged on Aug. 27, 1957. The patient remains out at this date and has shown no signs of returning psychosis.

This case is one of the rare, rather sudden and dramatic recoveries which form one of the most fascinating aspects of psychiatry. It was fortunate that this recovery began to take shape and went on to completion over a four-week period which closely coincided with a four-week period of intensified biochemical investigation of the Insulin Unit patients. During this time of steady clinical improvement the ratio of this patient's esterified to total serum cholesterol showed a continued upward adjustment toward the normal range (Fig. 2).

PATIENT 3.—This 26-year-old Negro man was admitted to this hospital Dec. 12, 1956. The patient had symptoms of schizophrenic reaction, paranoid in type. He was placed on ataraxics and showed little change in his mental status. He was transferred to the Insulin Unit on April 11, 1957. At that time he had a well-fixed delusional system and had evidences of a great amount of hostility and aggressiveness under rather rigid, brittle control. The patient was placed in the experimental placebo group and given sterile water.

During the time of the first intensified cholesterol study (July 15 to Aug. 5, 1957) the patient received this sterile water placebo. At this time the patient was showing moderate clinical improvement over the four-week period. He was beginning to have doubts about his delusional system. He lost some of his hostility and seemed able to ventilate his aggressiveness without fear of loss of control. During this period of clinical improvement he showed steady rise in the ratio of esters to total cholesterol toward the normal range.

In August and September this patient showed a rather marked increase in psychotic symptomatology. His delusional system returned in full force. He became very aggressive and acted out his hostility on frequent occasions. It was necessary to use supplementary sedatives and restraint in order to control him. During the intensified study in October and November, the patient again showed marked clinical improvement, and this was again concomitant with a steady rise of the ester-total cholesterol ratio toward normal levels. At the present time, the patient's disease has gone into a fair remission, and he is being considered for discharge. His ester-total cholesterol ratio is close to normal range (Fig. 2).

PATIENT 8.—This 41-year-old white man was admitted to the hospital on March 13, 1957. The patient had symptoms of schizophrenic reaction, paranoid in type. The psychosis was marked by disturbed behavior and well-organized delusions of persecution. The patient was placed on very high doses of ataractic drugs, with no change in his symptomatology. He was transferred on April 16 to the Insulin Unit and placed on regular insulin therapy. The patient showed continual slow improvement under the insulin therapy. In the period from July 15 to Aug. 5, his clinical state was undergoing steady improvement. In the same period his cholesterol ester ratio showed marked steady rise into normal levels. The patient was considered to be greatly improved at the end of this period and was placed on extended visit two weeks later. The patient remained out one month. During this time he showed progressive return to his psychotic symptomatology and became so disturbed and delusional that he attempted suicide. He was then returned to the hospital and brought back to the Insulin Unit. He was extremely depressed and hallucinative. He was again started on insulin therapy, on Oct. 15, 1957, which is the time during which intensified cholesterol studies had been started. The patient's cholesterol ratio showed a marked drop between the first two values and then even more marked increase to normal levels, and at this time he also showed steady clinical improvement. The patient is still on insulin therapy at the time of this report (Fig. 2).

PATIENT 10.—A 33-year-old white woman was admitted to the hospital on Sept. 17, 1956, with marked symptoms of schizophrenic reaction, catatonic in type. The major symptomatology was progressive, severe withdrawal with psychomotor retardation and marked blocking of speech. In the hospital the patient became mute and rigid and refused to eat. She was given a course of 22 electroshock treatments between Oct. 13 and Dec. 21, 1956, with slight lessening of withdrawal symptoms. She was transferred to the Insulin Unit on Jan. 27, 1957. At the time of admission to the unit, she was exhibiting early signs of reversion to muteness and inability to eat. Apparently, the moderate relief from symptoms after EST was only a transient effect. The patient was

placed on regular insulin therapy. She began to eat but continued to show withdrawal symptoms, psychomotor retardation, and blocking. During the period from July 15 to Aug. 5 the patient was described as showing marked catatonic elements, although these were less pronounced than when she had been admitted to the hospital. During this time her clinical course was steady. There was neither an increase nor a decrease in her symptomatology. Two weeks after the last biochemical study was done on this patient, she was brought to staff conference, was considered not ready to go home, and was transferred to a chronic building.

During a four-week period, when her clinical improvement was nil, this patient was showing a marked increase in the ester-total cholesterol ratio. Her values rose sharply and steadily from a low of 27% to a high of 67%, which is close to normal range. The patient seemed rather atypical in this respect, showing a marked rise toward normal range in her cholesterol ratios with no observable clinical change. It is interesting to note, however, that the patient subsequently went home on extended visit from a chronic service and, at the time of report, has remained out of the hospital for two months (Fig. 2).

PATIENT 13.—A 33-year-old Negro woman was admitted to the hospital Oct. 8, 1956. Upon admission the patient showed symptoms of schizophrenic reaction, paranoid in type. She had rather fixed delusional systems of persecution and generally operated according to this delusional system. She was placed on chlorpromazine (Thorazine). She became quiet and cooperative, did not express her delusional systems very often, and was placed on extended visit on Nov. 30, 1956. The patient returned 18 days later, again operating completely on the basis of a delusional system and, in addition, hallucinating. Her condition continued unchanged for the next three months, and she was admitted to the Insulin Unit on March 20. This patient was placed in an experimental placebo group and was given sterile water. She completed her placebo treatments on July 10 and was started on regular insulin treatment. In the next four weeks the patient showed moderate improvement under the insulin treatment. During this beginning phase of insulin coma therapy, and concomitant with rather moderate improvement, her ratio of esters to total cholesterol rose sharply from 34% to about 60% and then fluctuated in the low 60's and high 50's during the four-week period, extending from July 15 to Aug. 5, 1957. During the months of August and September the patient showed a resurgence of her psychotic manifestations. She again began hallucinating actively. She had to be taken off weekend visits to her home because of disturbed behavior, and it was necessary to administer supplementary sedatives and place her in restraint upon occasion. In October she began to show clinical improvement again, losing her disturbed, agitated behavior. During the test phase, occurring in October and November, the patient showed rather steady, continual clinical improvement, to the point where she was discharged from the hospital. During this same period of clinical improvement her cholesterol ratio showed a rather steady rise, from 40% to the mid-50's (Fig. 2).

PATIENT 18.—A 27-year-old white man was admitted to the hospital April 24, 1957. Upon admission the patient had symptoms of schizophrenic reaction, paranoid in type. He showed flatness and inappropriateness of affect. He had an air of suspiciousness and seclusiveness. He had some vague delusions of persecution, which later became rather well defined and well fixed. He was treated with ataractic drugs and showed some improvement in his mental status. In November, 1955, the patient was allowed out on extended visit from the hospital and remained away for one month. Upon his return, in December, 1955, he showed complete exacerbation of his psychosis. He was placed in a chronic building and remained there until Sept. 9, 1957, when he was transferred to the Insulin Unit.

On the Insulin Unit the patient has remained in approximately the same stage of psychosis, showing mild improvement and subsequent loss of this improvement from time to time.

During the period in October and November when his cholesterol ratios were being studied, he continued to show this fairly steady mental state. The cholesterol ratios showed fluctuation during the testing period, first dropping from 63% to 40%, then rising again to 68%, and finally falling to the mid-40's. None of this biochemical activity was reflected clinically in this patient, and he remains in about the same stage of psychosis at the time of report (Fig. 2).

Role of Liver

It is not our intention to indicate that cholesterol metabolism is either a cause or an effect of changing psychotic states, but, rather, to show that improvement in clinical symptomatology and rising cholesterol ester ratios parallel each other. But the findings compel one to reexamine the position of the liver in mental disease. It is of great significance that the liver must participate in the preparative steps of at least two metabolites which have been shown to be re-

quired for normal brain function. Serotonin has been shown to occupy a central role in the central nervous system.[14] However, serotonin cannot pass the blood-brain barrier under normal circumstances and is formed in situ from 5-hydroxytryptophan. This precursor of serotonin is able to penetrate the blood-brain barrier and is formed in the liver by the hydroxylation of tryptophan.[14] It has been suggested that this hydroxylation by liver is the limiting step in the formation of serotonin in the central nervous system.[14] Again, the liver plays an important role in the utilization of carbohydrate by the central nervous system. It is somehow necessary for the permeability of the brain cells to glucose,[15] and in the heptectomized animal glucose is unable to relieve insulin coma unless liver extracts are injected.[15] Furthermore, recent investigations have indicated that the liver is the site not only of the synthesis of free and esterified cholesterol but also of the destruction of these molecules.[6-8]

The foregoing statements lend considerable weight to the fact that variability in cholesterol metabolism may parallel alteration of other liver functions. Thus, the data in Table 2 show that a direct response of cholesterol metabolism to insulin in any week is a sharp drop in the E/T ratio (Fig. 1, *10-24, 11-14,* and *11-21*). This figure also shows the rapid return of E/T ratio toward the normal during the insulin-free period, Friday, p.m. to Monday, a.m. (Fig. 1, *11-21, 11-18*). Two other relationships are apparent; first, that over the entire course of treatment there is a general steady rise in the E/T ratio and that, as this occurs, the inversion effect disappears (Fig. 1); and, second, that, during the period studied, the weekly depression of E/T ratio in response to insulin becomes considerably lessened. The excellent correlation of the clinical course with the above relationships is good evidence that some functional activities of the liver are important in mental health and disease.

Thus, the present studies indicate at least two lines of further investigation. On the one hand, it is possible that there are several functions in liver which have a common enzyme system or systems necessary for the formation of particular metabolites, some of which may be necessary for normal brain function. An action of insulin may be a disturbance of this common system. But it is equally reasonable that certain endocrine or neurohumoral substances have regulatory effect at this same level in liver. Randall and Jellinek [4] have said that the adrenals are concerned in cholesterol metabolism in the liver. Insulin has been shown to have very definite effects on adrenal function. Thus, it is possible that the response of cholesterol metabolism in insulin therapy is an indirect result of the readjustment to insulin of mechanisms, as yet unidentified, which may be concerned with mental health and disease. The need for further investigation of the adrenohepatic area with respect to mental disease is indicated. Further clinicobiochemical investigations on this problem are in progress in this hospital.

Summary

The ratios of cholesterol ester and free cholesterol to total cholesterol (E/T and F/T) were studied in 27 patients undergoing deep insulin coma therapy over three successive testing periods. First, blood samples were drawn on four successive Monday mornings, following insulin-free weekends. Then, at a later date, specimens were drawn on a Monday, followed by specimens drawn Thursday in the same treatment week, and, finally, specimens were drawn on Thursday, Monday, and Thursday, in that order.

Studies of clinical ratings and the rise in E/T ratios showed good correlation with discharge rates among these patients. It is demonstrated that an immediate reaction of cholesterol metabolism to insulin in any treatment week is a depression of blood levels.

However, the effect over a course of insulin therapy is to reduce the depth of the immediate depression of the E/T ratio and to cause an ultimate elevation of the E/T ratios toward normal.

It is felt that serum cholesterol is not directly concerned in mental disease but, rather, that the response of cholesterol metabolism in insulin therapy is an indirect result of a readjustment of certain mechanisms caused by insulin. These mechanisms, as yet unidentified, may be concerned with normal functioning of the central nervous system.

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Lysergic Acid Diethylamide (LSD-25)

XXV. *Effect of Potassium Cyanide and Other Oxidase and Respiratory Inhibitors on the Siamese Fighting Fish*

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Although it is known that lysergic acid diethylamide (LSD-25) enters the brain, the mechanism by which LSD-25 acts to produce the psychotic patterns in man is unknown. Experiments which are designed to investigate the brain process in the intact animal might lead to a concept that could be developed to study the chemical process originating or connected with clinically occurring schizophrenia.

We have recently been studying the effect of potassium cyanide, sodium azide, hydrazine, and oxygen lack, among other respiration inhibitors, on an intact animal, the Siamese fighting fish. In addition, the action of oxidation-reduction indicators, like methylene blue, Bindschedler's green, and other dye systems, has been explored. It has previously been shown that the behavior of the Siamese fighting fish changes markedly in the presence of small doses of LSD-25 in the surrounding water.[1-3] It may now be reported that KCN and sodium azide act on the Siamese fighting fish in a way which is very similar to that of LSD-25. Hydrazine sulfate in much higher concentration was essentially without effect. However, anoxia and asphyxia can also produce reactions somewhat similar to that of LSD-25.

Method

The methods used were those previously described by Abramson and Evans[1,2] for the reaction of the Siamese fighting fish to LSD-25. For the purpose of this study, four of these, or related criteria, were usually chosen for analysis, as described by Abramson, Sklarofsky, Baron, and Gettner.[3] The main criterion utilized was the nose up-tail down position of the fish at the surface, at an angle of approximately 45 degrees or more. Rather important for the distinction between the enzyme poisons, like KCN and LSD-25, was the kink in the tail observed with LSD-25. It will appear that the respiratory inhibitors and anoxia did not usually produce this deformation. In addition, two negative criteria were used in the bioassay: (*a*) the number of fish at the top of the water which were not nose up, and (*b*) the number of fish at or near the bottom of the container. Observations were made usually every 15 or 30 minutes, as previously described, and the data plotted on standard bioassay curves for LSD-25, shown in Figure 1*A*.[2] In a typical experiment 10 fish were exposed to the drug studied in 100 to 200 ml. of water at about 80 F. The chemicals used, when available, were of reagent grade.

Experimental Study

The Effect of Potassium Cyanide.—With concentrations of potassium cyanide analogous to those used to obtain readily observable LSD-25 effects, i. e., 1 μg. per milliliter in the outside liquid, the fish, in general, act as if they were under a slightly lower concentration of LSD-25, rising to the surface and assuming a nose up-tail down position (Fig. 1*B*). The Cartesian-diver position is often assumed, although some of the motor characteristics of the LSD-25 effect are different. Casual inspection of fish under LSD-25 and potassium cyanide, as illustrated in Figure 2, might not reveal an important difference in the response. However, certain differences in the response are present, and a trained observer can distinguish between the effect of cyanide

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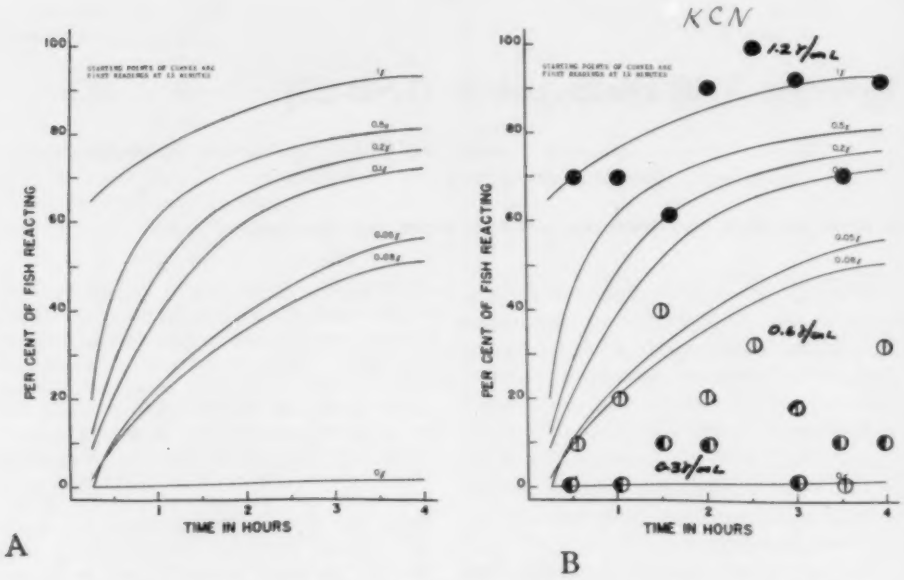

Fig. 1.—*A*, smoothed curves for the reaction-time curves of juvenile forms of the Siamese fighting fish response to LSD-25. The numbers above each curve represent micrograms of LSD-25 per milliliter in the outside liquid.

B, responses of the Siamese fighting fish to potassium cyanide as plotted using the standard curves illustrated in *A* as reference. The concentrations of potassium cyanide in the outside liquid were 1.2μg., 0.6μg., and 0.3μg. per milliliter.

and the effect of LSD-25, especially by the absence of the kinking of the tail. There are other differences. For example, the excitatory stage does not occur under KCN unless the fish are exposed to higher concentrations. The fish are usually more quiescent under low doses of KCN. If the fish are disturbed and moved to other parts of the containing vessel by shaking, they usually do not rise to the top as soon as those under LSD-25 do. However, the display of the fins of fish exposed to 1μg. of KCN per milliliter is more evident. There is a greater swelling in the gill region under KCN. Apparently, the KCN is utilized more rapidly than is LSD-25 by the fish, for if the fish are transferred to fresh water, they recover faster from the KCN than they do from LSD-25. The accompanying Table illustrates experiments showing the effect of concentration of KCN on the Siamese fighting fish. This varied slightly from experiment to experiment. Since the molecular weight of LSD-25 is about five times that of KCN, it would appear that the number of KCN molecules required is somewhat greater than that of LSD-25 molecules available for the reaction. The observation that the fish recover more quickly from KCN than from LSD-25 is suggestive that factors of metabolism may be more important than the initial dose, since the two reactions occur at molarities that are close. The approxi-

Fig. 2.—Comparison of the effect of LSD-25 and potassium cyanide on the behavior of the Siamese fighting fish. In general, the fish behave under potassium cyanide like those under LSD-25.

*Effect of Varying Concentrations of KCN on the Siamese Fighting Fish**

Time	I KCN 1μg./Ml.	II KCN 0.2μg./Ml.	IIa KCN 1μg./Ml.	III KCN 0.1μg./Ml.	IIIa KCN 1μg./Ml.	IIIb KCN 1μg./Ml.	IV KCN 1μg./Ml.	IVa $NaNO_2$ 50μg./Ml. KCN 1μg./Ml.	V KCN 1μg./Ml.	VI KCN 0.5μg./Ml.	VIa $NaNO_2$ 50μg./Ml. KCN 0.5μg./Ml.	VIb $Na_2S_2O_3$ 100μg./Ml. KCN 0.5μg./Ml.	VII KCN 1μg./Ml.	VIIa KCN 0.1μg./Ml.
0	0	0	0	0	0	0	0	0	0	0	2	1	0	0
15 min.	4	0	6	0	6	9	5	7	3	2	3	3	0	0
30 min.	7	0	9	0	5	3	7	5	6	3	8	2	0	0
45 min.	9	0	9	0	6	4	6	7	7	3	6	3	2	0
1 hr.	8	0	9	0	10	6	6	7	7	2	7	3	4	0
1½ hr.	8	0	10	0	10	5	8	10	9	3	6	5	4	0
2 hr.	8	0	8	0	10	8			7	3	6	5	5	0
2½ hr.	8	0	9	1	10				4	3	6	6	3	0
3 hr.	10	0	9	0	8				6	5	5	5	4	0
3½ hr.	10	0	8	0	8				5				3	0
4 hr.	9	0							5				7	1

* Note, in addition, that $NaNO_2$ and $Na_2S_2O_3$ do not block the action of KCN. In Experiments VIa and VIb the fish were exposed to $NaNO_2$ and $Na_2S_2O_3$ for one hour and then transferred at zero time to the solution containing potassium cyanide. The numbers refer to the number of fish nose up-tail down at the surface, the criterion used for the effect of LSD-25.

mate molarity of KCN in the outside liquid at 1μg. per milliliter is 1.5×10^{-5} M. However, decreased reactions were occasionally observed at lower concentrations as well as at 1μg. per milliliter. For example, 1μg. of KCN per milliliter might act more like 0.5μg. of LSD-25. The Table shows not only the variation of our observations but also the absence of effect of certain antidotes to KCN. Only the criterion of nose up-tail down is given in order to abbreviate the data. It is possible that the discrepancies insofar as concentration effects are concerned may be due to inactivation of the KCN in the outside liquid by excreta, variation in O_2 tension, or other metabolic factors.

Effect of Other Oxidase Inhibitors.—Hydrogen sulfide at high concentrations (100μg. per milliliter) was lethal, but the surviving fish assumed a nose up-tail down position at the surface. The effect of hydroxylamine hydrochloride up to concentrations of 100μg. per milliliter, as well as of hydrazine sulfate up to 10μg. per milliliter has thus far been negative. Most interesting was the effect of azide. Figure 3 illustrates an experiment with sodium azide. Although sodium azide is more toxic than potassium cyanide, an effect analogous to that of LSD-25 is readily observed at concentrations of sodium azide similar to those observed for LSD-25.

Anoxia and Asphyxia.—Preliminary data indicate that a decreased oxygen supply with simultaneous prevention of accumulation of carbon dioxide resulted in the nose up-tail down position similar to that for LSD-25 in several hours, the fish remaining alive. When carbon dioxide was permitted to accumulate in the absence of renewed oxygen, all the fish assumed the nose up-tail down position in several hours. The fish rose rapidly to the surface when disturbed. Recovery was rapid from both anoxia and asphyxia. Experiments are in progress with improved techniques of observation.

Fig. 3.—Effect of sodium azide on the Siamese fighting fish compared with that of hydrazine sulfate in the outside liquid. Sodium azide acts similarly to potassium cyanide and LSD-25, whereas hydrazine sulfate is without effect.

Oxidation-Reduction Indicators and Other Dyes.—A concentration of methylene blue of 100μg. per milliliter produced a suggessive LSD-25 reaction. Bindschedler's green affected the fish, producing a noticeable excitatory period; 20μg. per milliliter produced the nose up-tail down position with no kink in the tail. In a comparative experiment, 20μg. of Bindschedler's green per milliliter was more effective than 1μg. of potassium cyanide. It is of interest that the effect of methylene blue increased with time. Fifty micrograms of toluylene blue and indigo disulfonate per milliliter were without an important effect. Fifty micrograms of indigo tetrasulfonate per milliliter was also ineffective. Sodium-2,6-dichlorobenzene indophenol was effective, the effect increasing with the concentration up to 50μg. per milliliter, where an effect equivalent to 1μg. of LSD-25 per milliliter was observed. Although 50μg. each of gentian violet and methyl violet per milliliter killed the fish, lower concentrations, 20μg. of each per milliliter, produced a nose up-tail down position in more than half of the fish at the end of four hours.

We are not prepared to say what mechanisms are involved in this series of experiments with dyestuffs. In view of the results with oxidase inhibitors and anoxia, it was tempting at first to believe that the dyes might act by interfering with oxidation processes. However, although enzyme inhibition may be involved with oxidation-reduction dyes, the fact that the dyes were not injected, but had to pass through the mucous membranes, complicated the proc-

ess. The positive effect with dyes like methyl violet and gentian violet may be due to gill injury and anoxia rather than enzyme poisoning. In favor of this is the observation that potassium permanganate produced an LSD-25-like reaction, which decreased with time as the potassium permanganate was chemically reduced in the water surrounding the fish. However, a response somewhat similar to that with LSD-25 may be obtained if the total dose of 10μg. per milliliter is added to the water in fractional quantities.

Comment

It has often been observed that human subjects under the influence of comparatively small doses of LSD-25 have the confusion and other symptoms that are associated with anoxia. The effects of LSD-25 in man, therefore, are not incompatible with the assumption that LSD-25 in the fish and in man acts by poisoning some parts of the enzymatic processes connected with oxidation. Although at the time that this report was made we have not had access to the data dealing with the effects of nonlethal doses of potassium cyanide on the mental state of man, the available data in the literature indicate that an exogenous psychosis, with loss of reality sense, is produced with nonlethal doses. Indeed, potassium cyanide has been used in the therapy of schizophrenia, apparently to stimulate the respiratory enzymes. It is worth while, on the basis of these data, to explore the possibility not only that the LSD-25 psychosis in man may be connected with poisoning of special oxidative enzymes but also that the schizophrenic process may be connected with a similar process, where special respiratory enzymes of the brain are not functioning adequately.

Bain[4] has recently reviewed the biochemical effects in vitro of certain psychotomimetic agents. He and his co-workers, as well as Clark and his co-workers, report on the effect of LSD-25 in vitro. Among the systems studied was cytochrome oxidase from brain, glucose oxidation by unstimulated rabbit brain slices, and glucose oxidation by dinitrophenol-stimulated rabbit brain slices, as well as oxidative phosphorylation in rat brain or liver mitochondria. Only slight inhibition of oxidation of glucose by rabbit brain was observed for LSD. Mitrochondrial preparations of brain tissue are not sensitive to LSD under certain conditions. Although LSD does not act like cyanide on certain in vitro systems, the number of metal-enzyme catalysts and catalyst systems existing in vivo make this aspect of the subject open for future intensive study.[5]

Perhaps shock therapy nonspecifically stimulates the oxidase and allied systems in the brain. Experiments designed to study the effect of substances which might modify the functioning of the oxidase systems in the brain are being planned on the basis of the foregoing experiments. It is hoped that along this path of investigation the schizophrenic process in man may be ultimately modified in the direction of recovery.

Summary

The effect of potassium cyanide, sodium azide, hydrazine, and oxygen lack has been studied on an intact animal, the Siamese fighting fish. In addition, the action of oxidation-reduction indicator systems and other dyes has been explored.

Potassium cyanide and sodium azide in nonlethal concentrations of approximately 1μg. per milliliter in the outside liquid act similarly to LSD-25, with minor differences. Negative results were obtained for hydrazine sulfate and hydroxylamine hydrochloride in much higher concentrations.

The action of potassium cyanide is reversible, with the fish recovering more rapidly than under similar concentrations of LSD-25.

Anoxia and asphyxia produce the nose up-tail down position characteristic of LSD-25. This reaction is reversible.

High concentrations of certain dyes like methylene blue, Bindschedler's green, and

sodium-2, 6-dichlorobenzene indophenol produced similar phenomena. Effects were also produced by gentian violet and methyl violet. It is believed these phenomena are connected with anoxia.

In view of the fact that human subjects under small doses of LSD-25 experience the confusion and other symptoms associated with anoxia, it is proposed that these experiments on fish with enzyme inhibitors may lead to an understanding of the exogenous psychosis produced in man by LSD-25, through a further study of the possible metal-enzyme systems poisoned by potassium cyanide and sodium azide.

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Psychoanalytic Orientation in Psychotherapy

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A general discussion of the psychoanalytic orientation in psychotherapy may encompass all of psychotherapy or be limited to more modest aims. In this paper an attempt will be made to define terms, to differentiate the psychoanalytic orientation in psychotherapy from other orientations, to describe briefly the techniques of this form of therapy, and to differentiate these techniques from the technique of psychoanalysis. Modifying somewhat the definition formulated in a previous paper,[1] I regard psychotherapy as an organized, conscious, purposeful, scientific effort on the part of the therapist to influence by psychological methods, i. e., primarily by words and behavior, the state of mind (and of body) of a patient, to the end that symptoms and disease syndromes may be ameliorated or cured. What the therapist does may be active, in the sense of doing something to the patient, or passive, as in listening to the patient; but, in either event, it is purposeful. To deserve the name scientific, the treatment must be based on scientific principles or method. As Hart[2] has noted: "Everybody is aware that science is a method of acquiring knowledge but everybody is not aware that this method is always one and the same whatever the subject may be to which it is applied." Following Karl Pearson, he describes the scientific method as consisting of three steps: (1) the collecting and recording of facts; (2) the classification of these facts into series or sequences, and (3) the evolvement of a formula or scientific law which will permit a description of the sequences of fact in the most comprehensive and convenient manner. The third step comprises a scientific law, theory, or frame of reference.

Psychoanalysis, evolved by the scientific method, is the term Freud[3] used for his scientific theory of psychopathology. This theory developed concurrently with the technique of psychoanalytic treatment, which was also used as an investigative tool. A discussion of the investigative aspect will be omitted from this paper.* The psychoanalytic orientation in psychotherapy refers primarily to the employment of psychoanalytic theory, as a frame of reference, regardless of what techniques are used. The technique of psychoanalysis naturally rests on psychoanalytic theory, but psychoanalytically oriented psychotherapy, while it is grounded also in this theory, is not, or should not be, primarily concerned with psychoanalytic technique.

Psychoanalytic theory states that all psychic events occurring at any point in time, true to the laws of causality, have connections and continuity with all past psychic events. This is known as the law of psychic determinism. Since these aspects of psychic continuity are not always conscious, yet easily observed, they could only be explained by deducing the unconscious. The nature of the unconscious is such that impulses may arise in it which enter into conflict with learned patterns of behavior. This conflict may give rise to symptoms.

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* The term "psychoanalysis" should be used in no other way, although one occasionally hears lay persons use the term erroneously to mean "mind reading" or "diagnosis of a psychiatric condition."

These represent a compromise solution to the problem of satisfying both the basic urges and the forces which oppose them.

The origin of both the urges whose satisfaction is forbidden and those which are permitted satisfaction lies in the individual's biology. In psychoanalytic theory, an *instinct* is defined as a drive which has its source in the physiology and chemistry of an organism; whose aim, in every instance, is satisfaction, and which requires an object through which it may achieve its aim. There are two main groups of instincts: (*a*) libido, which refers to the binding, self-preservative, and race-preservative (i. e., sexual) group, and (*b*) the aggressive, destructive group, sometimes called *mortido, thanatos,* or death instinct. These instinctual urges never exist in pure form but function in an admixture of fusion of one with the other in varying quantities.

The *ego* is a differentiation of the id which is specially developed under the influence of the real, external world (i. e., what is done to the child by caretakers and what happens under other aspects of the child's environment). It acts as an intermediary between the id and the external world. There are two main characteristics of the ego: (1) It controls voluntary movement as a consequence of the relation between perception and muscular action, and (2) it operates in the service of self-preservation through adaptation to external events (flight, fight, or surrender) and through control over the instincts (allowing satisfaction, postponing satisfaction, or suppressing the excitations altogether).

The *superego* is a special agency in the ego; it is the moral precipitate left behind from the long period of childhood during which the growing human being lives in dependence upon his parents and is the instrumentality through which parental and similar societal influences are prolonged into adult life. The superego is determined by the personality of the parents and caretakers, by the traditions of race, nation, and family, including successors and substitutes of the parents, and by the examples of high social ideals. The conscience is the conscious part of the superego. The remainder of the superego is unconscious and consists of a sense of *mustness* or *oughtness.*

Every action of the ego must satisfy the demands of the id, the superego, and reality. When instinct tensions increase and satisfaction is withheld, a sense of unpleasure is experienced. A lowering of instinct tensions is felt as pleasure.[4]

Psychoanalytic theory defines neurosis as the expression in symptoms of an internal conflict between the ego and its internal antagonists, the id and the superego. The symptoms are determined both by the presence of the signal of danger and by the particular method of defense used by the ego to ward off the (fantasied) danger. These methods of defense may have been successful in the past personal history (childhood) of the individual, but they may no longer be appropriate. Neurosis arises when an external situation (reality) disturbs the equilibrium (adaptation) of the person and awakens old desires which are considered to be dangerous. Neurotic behavior is inappropriate when past patterns employed in the present meet conditions different from those of the past (Fenichel[5]).

The psychological structure of a psychosis is somewhat similar, but a psychosis differs from a neurosis in two essential respects: (*a*) There is, in the psychotic individual, a difference in constitution, that is, in the strength of his instincts and his ability to cope with them, and (*b*) the defenses (nature of the defense mechanism) which the environment has engrafted on the psychotic individual are particularly inappropriate or unsuccessful. The development of a psychosis is influenced in added ways by the individual's personal development and the nature of the conflict. Glover[6] feels that the period of psychosexual development in which the disturbance occurs is important in differentiating the nature of the reaction. In psychosis the ego disturbance occurs in the first three years of life, while in the neurosis the disturbed

psychosexual development takes place in the years from 3 to 6.

Freud's observation [7] that neurotics tend to use patterns out of the past led to his discovery of transference. He defined transference as that phenomenon whereby a patient experiences toward the physician "emotions and fantasies which are new editions or facsimilies of emotions or fantasies previously experienced towards a person intimately connected with the patient's past life" (especially his childhood). Transference is a spontaneous phenomenon, repetitively lived out as an emotional and behavioral experience, with the complete repression (i. e., forgetting) of the original experience. Transference phenomena have the same meaning for patients as post-hypnotic suggestions. The transference emotions and behavior are attached to ideas other than those to which they belong. The patient may rationalize and feel somewhat uncomfortable about his behavior, but he does not fully understand it. "He expresses the repressed in action but not in memory," [1] (Nunberg [8] has clarified and emphasized the projective, externalizing nature of transference.)

The core of all psychotherapy is transference. The psychotherapeutic influence which Mesmer exerted was based on the frame of reference of physics, but it was suggestion working through transference that was operating. When the physical frame of reference was discarded and hypnotism was substituted, it did not alter the transference significance. The understanding of transference is implicit in the psychoanalytic orientation in psychotherapy. (The difficulty of treating psychotic patients psychotherapeutically is due to transference patterns repeating too exactly the overwhelming traumatic experiences of too early childhood.)

A few years ago, the Group for the Advancement of Psychiatry attempted to formulate an empirical frame of reference designed to focus discussion on the therapeutic interaction between patient and physician. This formulation defined psychiatric and personality disorders as the failure of adaptation of a human being which has conscious and unconscious historical genesis, and which appeared insidiously (beginning early) or acutely, precipitated by the appearance of a task which exceeded the person's capacity for mastery at the given time and under the given circumstances. (In the effort to cope with the problem, the previous equilibrium was disturbed, and inner conflicts and tensions result. Anxiety is the chief signal of such conflict and tension.) This formulation is based on the psychoanalytic frame of reference and recommends that any program of psychotherapy should take that frame of reference into consideration.

Psychotherapy is then defined as a progressive interaction between patient and therapist during the course of which there develops on the part of the patient what has been designated as a transference neurosis. This comprises verbal and nonverbal communications which relate both the conscious and the unconscious repetitions of current and previous conflicts and the problems and modes of adaptation with some attempt at reenactment of these events in the treatment situation. There develops reciprocally on the part of the physician conscious and unconscious, verbal and nonverbal reactions to the patient and his illness, as well as planned techniques which influence the course of the treatment. Out of these interactions in the treatment process, opportunities are engendered for discovering more adequate biological and social solutions, which are tested, learned, and applied.

It is my belief that this formulation applies to the technique of *psychoanalysis* rather than to *psychotherapy*. Freud [9] once said (in a report for the Austrian Medical Commission investigating the psychiatric methods of the Austrian Medical Corps in World War I) that the technique of psychoanalysis could not be practiced in military psychiatry but a knowledge of psychoanalytic theory would have been helpful. (That this statement was true was amply borne out by experiences in military psychiatry in

the American services in World War II). First, the mechanism of production of psychiatric illness, particularly neurosis, was better understood; second, a key to the comprehension of the previously nonintelligible communications, both verbal and nonverbal, of psychotic, as well as neurotic, patients was more readily available, and, third, the efforts of physicians did not need to be wasted or misused through ignorance; hence their therapeutic influence could be applied in a rational way.

Bibring [10] has referred to a purposive typified behavior on the part of the therapist as common to all methods of psychotherapy regardless of their frame of reference. He described four principal types of therapeutic operation: (1) the production of material primarily through verbalization, but also through nonverbal communication; (2) the utilization of the produced material, mainly by the therapist, who attempts to understand it, but also by the patient, whose verbalization may facilitate his own understanding, or who may obtain relief from the act of self-expression, or from the transference; (3) the assimilation by the patient of the results of the preceding operation, to carry the treatment further to the next stage of understanding and/or by experiencing relief; (4) the initiation and carrying out by the patient of changes in real life resulting from these processes of reorientation and readjustment.

Applying these four principles to the technique of psychoanalysis, (1) material is gathered through verbalization by free association; (2) the analyst understands the material and groups, clarifies, and interprets it; (3) the patient reacts to the interpretation (when correct and understood) by the production of additional material, entering more deeply into older, repressed patterns (controlled regression confined to the analytic hour); (4) reorientation and adjustment occur automatically through the necessity for living out transference reactions being obviated.

In psychoanalytically oriented psychotherapy, free association may start off the entire treatment or any particular treatment session, or be a part of a session, but it is not required or expected to proceed as is done in psychoanalysis. Controlled regression is not the aim of psychotherapy, as it is of psychoanalysis. The material in psychotherapy is focused on actual facts (reality) more than on fantasy. The therapist constantly weighs reality in the patient's production of material and focuses attention on it, discussing it at every opportunity with the patient. Regression is tactfully discouraged through avoiding free association, ignoring dreams (or doing very little with them), and avoiding deep interpretations (i. e., connections with the infantile neurosis). The patient experiences a meaningful sense of conviction on the level of reality, apart from the transference, as well as through the behavior of the therapist, which is clearly different from that of the transference image. Reorientation and readjustment are suggested, advised, and encouraged.

The goal of psychoanalysis is the elimination of the infantile neurosis through the transference neurosis, which is systematically interpreted and put into words. What is unconscious must be made conscious. Recall of forgotten, repressed events must occur along with realization of how the past differed from the present. Insight with the capacity to attach words to concepts and feelings is a requisite for a successful psychoanalysis. Restoration of function is a by-product rather than a direct aim.

The direct goal of psychotherapy is the restoration of function by whatever means is possible. This goal may be accomplished with or without insight, and most frequently insight is absent. Reviewing the list (a modification of Bibring's classification [10]) of six main psychotherapeutic techniques (in contradistinction to the psychoanalytic technique), fully the first five are able to produce psychotherapeutic effect without requiring insight, and even in the sixth the insight is on a different level from that of psycho-

analytic insight.† The six groups of psychoanalytically oriented psychotherapy are (1) therapy by patients' transferences; (2) therapy by patients' substitutions; (3) suggestion employed by the therapist; (4) abreaction by the patient to the therapist; (5) employment by the therapist of the patient's emotional apparatus for technical or therapeutic purposes, or to test reality (I call this "ployment"); (6) clarification by the therapist of the denominators common to the patient's reaction patterns.

The techniques of (1) transference and (2) substitution may be effective without a trained therapist.‡ Without quite knowing what they are doing, patients may establish therapeutic transference relationships with many different people: family doctors, lawyers, religious leaders, teachers, lecturers, and friends. These relationships may suffice to enable the patient to maintain a successful adaptation, and the underlying psychiatric illness may then become apparent only when an accident of fate suddenly removes the transference object. The following case history is an example.

Case 1.—An 18-year-old girl came for treatment because of extreme anxieties and phobias on her first job, which had been obtained for her by her friend, Alice. Although she had had a difficult childhood (her father worked 16 hours a day, 6 days a week, from the time of her birth and hence she rarely saw him, and her mother had helped in the store from the time the patient was 11 years old), she nevertheless stated that she had not been unhappy. She had heard that her sister, eight years older, had been extremely resentful of her birth and had thrown her out of a third-story window when she was 3 (fortunately, without serious effect). But she stated that of recent years she had gotten along with her sister and brother. She had many good friends and tended to choose them from among girls who had warm parents who dined nightly with their children and were at home on weekends. She had had some attacks of phobias (for trains) and other anxieties, and depression, but was always able to talk them out with her best friend, Polly. Polly was like a good sister. Disturbing sexual conflicts were discussed with Polly, who always counseled continence.

Her present illness began about a month after she learned that Polly, who had suddenly married her "steady" boy friend and moved away, was about to have a baby. Others had talked about it, and the patient had protected her friend. The trauma was a double one. Not only had she lost her transference object through separation by distance, but the loss was made worse by her feeling of having been betrayed. Her new-found job became threatening because it called for another relationship with a friend (who represented the danger of hurt, as Polly had hurt her). On the patient's side, there was the danger of escaping revenge feelings. Old aggressive feelings toward mother and sister were revived. If Polly's betrayal had not occurred, this patient might well have been able to adapt to her neurosis on the basis of repeated transference relationships of the same kind.

The patient was brought, with difficulty, to a satisfactory rapport. She began to improve when she learned that her halting communications in treatment would not be looked upon as her failure. The therapist's imperviousness to her unconscious aggressive impulses also promoted confidence, with further progress toward the establishment of a positive transference.

Substitution refers to the capacity of patients to exchange one set of symptoms for another. Glover [11] suggested that when an internist or a general practitioner ignores a patient's psychic conflicts and suggests a holiday, taking up a sport, like golf, or a mental activity, such as attending concerts,

† This does not imply that psychoanalysis is the "best" form of treatment because it engenders insight, or that psychotherapy is "second-rate" therapy. It merely asserts that insight is of varying importance at different levels in the various psychiatric conditions. A successful cure by suggestion might be jeopardized by insight. Nor is it necessary to explain in words a conviction won by experience. In some conditions and in some people, such verbalization might vitiate the emotional convictions. In fairness to the technique of psychoanalysis, however, it should be stated that when properly employed in suitable cases, the insight derived from psychoanalysis proves to be the only efficacious treatment.

‡ The frequency of "transference cures" in the most complex treatment situations is well known; it is truly impossible to state the extent of therapeutic effect which occurs as a result of these two techniques in many dynamic therapeutic relationships. (Intellectual) acquiescence to interpretations may be given the credit for cure when the actual reason for improvement was the establishment of a warm relationship with or without an increase in repression or shift in defensive structures. This is especially true in the treatment of psychotic patients or of patients with certain psychosomatic disorders.

he is inciting substitution of symptom formation. Patients frequently discover this form of treatment for themselves. The anxiety-binding function of a hobby deserves more notice than it usually gets. The obsessional hobbyist often uses his hobby in an adaptive way to express his obsessional neurosis. In some instances, religion serves a similar function. A specific example, slightly different from the aforementioned, may be seen in Case 2.

Case 2.—A young married woman, the mother of two children, consulted me about six years ago with complaints of phobias, depression, and a tendency to progressive drinking, which was disturbing her. She was an attractive and intelligent woman who had been brought up in a parental atmosphere of emotional neglect and material overindulgence. She had been seen by several psychiatrists previously but had been unable to establish a satisfactory working relationship with any. I suggested that she try psychoanalysis, having in mind that if she accepted, it would be on the healthy basis of agreeing to enter into a long-term relationship. I also counted on my ability to analyze her transference resistance and her acting out. She refused this suggestion, however, and subsequently told the referring physician that she found me too cold. I heard that she later tried one or two other psychiatrists but did not stay in psychotherapy through any adequate span.

A few weeks ago, she called for an appointment. She wanted advice on how handle a delicate matter which was threatening to disturb the equilibrium of her home. She had initiated a flirtation with the husband of a dear friend and was afraid it was getting out of control on his part. Her position with her friend was jeopardized, as was her position as a respectable married woman in her own social circle. She stated that she was not at all sick, had no symptoms, and was well and happy. She had discovered that she could have just what she wanted by flirting and taking lovers while simultaneously carrying out her duties as a seemingly devoted mother and dutiful wife. She was no longer phobic, and her drinking, which had decreased along with the decrease in her anxiety and depression, was now confined to social occasions. Unhappiness came to her only when her desires were not gratified.

This patient had apparently solved her psychiatric problems by substituting for her symptoms, a neurotic pattern of action which she preferred because of primary and secondary pleasure gains. It is interesting that most seemingly successful substitutions exchange mental symptoms for some form of (neurotic) action. (This has implications for understanding the acting out of neurotics and the difficulty of handling patients' acting out in any treatment.)

While transference and substitution may be effective without a trained person, the other techniques usually require a psychotherapist. Suggestions may be used to patients by people other than *trained* psychotherapists, but the patient endows the suggester with therapeutic powers. Similarly, abreaction may occur in other than actual treatment situations, but, again, it is efficacious only when the transference object is endowed by the patient with the power to heal.

The technique of suggestion hardly needs elaboration. It is the commonest technique of psychotherapy and accompanies many other psychotherapeutic techniques. It is used both as a technical device in the service of other techniques and as a therapeutic technique in itself. (It is the main ingredient in hypnosis.) It operates in direct positive ways, in indirect positive ways, and in negative ways. To a phobic patient, "Don't be afraid" is a direct positive suggestion; to a patient with an anxiety neurosis "Stop worrying" is. Indirect positive suggestions are nonverbal and distracting, such as, for example, medical procedures which produce a psychotherapeutic effect independent of the drug or procedure used; a physical examination which is negative indirectly suggests "Therefore stop worrying." A prescription of medicine or an injection of vitamin B_1 suggests, "You are now cured." A negative suggestion is also present in ignoring the psychic conflict. The internist who treats a conversion symptom, or its anxiety equivalent, as though it were an organic disease, prescribing medicine on that basis, is in effect suggesting that the conflict be ignored (i. e., repressed). Avoiding comment on a dream which a patient brings is a tacit suggestion to ignore it. Successful suggestion operates by the device of the patient relinquishing

certain of his ego and superego functions and turning them over to the therapist. On the part of the ego, it is the function of reality testing § which is temporarily transferred. On the part of the superego, it is the function of critical self-judgment. In the psychoanalytic orientation, the requirements for using the technique of suggestion are that the therapist know what he is doing, that he understands transference, and that he do what he does purposefully, and deliberately.

An example of the use of suggestion in the service of other psychotherapeutic techniques is the suggestion to speak frankly. This facilitates emotional expression by the patient, as well as the gathering by the therapist of material necessary for insight. Suggestion is used in psychoanalytic technique to overcome certain forms of resistance,‖ to produce recollections, fantasies, dreams, and imaginary or symbolic conflicts. It may appear in the course of a psychoanalysis as an "active" technique of having a patient face his phobia or relinquish his compulsion. (This is also a "ployment," as will be explained below.) When used as a technical device, suggestion by itself does not produce a psychotherapeutic effect. In these instances the therapeutic effect eventuates from ultimate abreaction, corrective experience, clarification, or insight.

Abreaction refers to emotional release or discharge of emotional tension. The technique occupies an important place historically in psychoanalytic psychiatry, since it was a vital part of the cathartic method employed early by Breuer and Freud.[13] It is based on the theory that "dammed-up tensions which have found abnormal discharge (as in symptoms) must be revived in memory and the normal expression reestablished mainly in the form of emotionally charged verbalization." Bibring [10] feels that abreaction cannot be curative by itself. Perhaps it would be more correct to say that abreaction in a therapeutic situation never takes place by itself. Various therapeutic principles other than abreaction are certainly involved in the process of emotional expression: (1) Verbalizing thoughts, feelings, and impulses enables one to see reality more clearly; (2) the experience of being listened to brings gratifying feelings of being accepted and understood; (3) unconscious gratifications of a narcissistic and exhibitionistic nature may occur.[10]

The following case is an example of abreaction.

CASE 3.—A patient with pernicious vomiting of (her second) pregnancy was referred for psychotherapy after failure of all physical measures. She had had a similar difficulty before the birth of her first child, a daughter. She was much concerned that her second child might also be a daughter. With considerable difficulty, accompanied by much emotion, she told of having had a premarital sexual experience, of which she was ashamed. She stated that she had never told this to anyone and was disturbed because it made her feel ashamed before her daughter. On her second visit she related that she had not told the whole truth, but felt much better after the visit. She then confessed to several premarital experiences and stated that she would not want her daughter to be like that. It occurred to her that she might have another daughter, and it was so important for a mother to set a good example for her daughters. Clearly, there was an element of magic in the feeling that she would be punished for being "bad" by her daughters' going bad. After telling this she felt there was nothing more to say and that she would not need further treatment. While the patient was not completely cured, I learned from her obstetrician that her vomiting had decreased considerably. There were obviously deeper roots of neurosis in this hysterical patient which she was loathe to unearth. The relief of acute distress, even though only partial, was sufficient for her, and she ac-

§ Reality testing is a function of the ego which enables the individual to discriminate between facts or factual events and fantasy. "With the development of the reality principle, the ego learns that it protects itself best against threats and procures a maximum of gratification if it judges reality objectively and directs its actions accordingly" (Fenichel,[8] p. 508; Freud [12]).

‖ Resistance is a term used by psychoanalysis to indicate those dynamic forces which serve to oppose the emergence into consciousness of unconscious ideas and impulses. It is manifested by certain defense mechanisms which become obstructive during psychoanalysis and some other dynamic psychotherapies.

cepted the compromise solution in place of further exploration.

The following case may be given as a more complex example of abreaction coupled with an emotional readjustment in the transference.

CASE 4.¶—A German refugee had come to the Mount Sinai Hospital psychiatric clinic with multiple complaints of severe headaches, buzzing, and gastrointestinal difficulties. He improved with treatment until only one symptom remained—difficulty in swallowing. In the course of his treatment he had told, without emotion, how bad he had felt because he had been unable to share some of his food with his father on the way to the concentration camp. The therapist suggested to him that he bring a sandwich to the next therapy session, at which time the therapist ate a part of the sandwich. This time the patient recalled the concentration-camp experience with considerable emotion and subsequently was able to swallow.

The psychotherapeutic effect in this case was probably achieved by something more than "relief because of discharge of emotional tension." It was also partly a "corrective emotional experience," to use Alexander's term.[14] Bibring[10] has designated as "manipulation" the employment of a patient's emotional systems for the purpose of achieving therapeutic change, whether in the technical sense of promoting the treatment or in the curative sense. Bibring's term encompasses Alexander's concept, but is too ambiguous and is apt to be confused with terms like "manipulation of the environment" and "manipulation of the transference" (role taking). To avoid such misunderstanding of "manipulation," and also the one-sidedness of preempting a generic term for a specific technique, I would suggest that, for this whole group of technical measures, we use the term "emotional ployment and replayment." A "ployment" is what the therapist does; a "replayment" is the patient's reaction. The term emotional ployment would thus be appropriate for any of that group of therapeutic techniques which operate through the attachment of a patient's emotional charges on a more realistic basis to impulses, actions, and attitudes.

Through the medium of the transference, the patient lives out a repetition of the drama of his neurosis, but now it has a different ending. He thus experiences a corrective emotional replayment. The function of reality testing is promoted. It is likewise augmented by education, which plays an important part in all the therapies. In emotional ployment, the patient's superego is invoked positively in the service of treatment as a technical measure to produce a favorable attitude toward treatment, or negatively to remove obstructive trends.

The following case history is illustrative of the technical aspects of positive and negative ployment and of therapeutic ployment and replayment.

CASE 5.—A 25-year-old single professional man came for treatment because his parents, enlightened professional people who had had treatment themselves, insisted that he go. He had drifted into a relationship with a girl of questionable character, and his parents disapproved of the marriage on the grounds that this was a neurotic choice which would ultimately injure the patient. As a result of the conflict with his parents, the patient had developed severe anxiety, irritability, and a tendency to reckless behavior, particularly when driving. He consented to being treated only partly because he was suffering; he actually resented having been forced into treatment by his parents against his will, and he was concerned lest the therapist might likewise force him into accepting things against his will. The patient was given to understand that whether or not he entered treatment was his decision alone, although his doing so would mean an indefinite postponement of his marriage plans. He was also told that he was not required to accept any explanation unless he was convinced of its validity, as well as of the soundness of the evidence in support of it.

The positive ployment operated through neutralizing his anxiety about being influenced against his will. The negative ployment served to remove obstructive trends to treatment by neutralizing his resentment. Curative ployment and replayment occurred when the patient experienced something new in his relationship with the therapist. He had come for treatment less out of a desire to be helped than because of a necessity to please his parental authority figures. When the therapist helped him to feel competent to act on his own,

¶ The therapist in this case was Dr. Emery I. Wells. I was Chief of Clinic at the time the patient was being treated and was thus able to follow the case closely.

the patient's desire to please the therapist influenced him in the direction of assuming responsibility. A curative reployment took place as the patient experienced in the transference an authority who expected independence rather than submission. Such new experiences help the patient learn that he can behave independently not only in the transference (treatment situation) but also in life, in relation both to himself and to others.

Various additional examples of ployment may be given. It is a positive technical ployment when a phobia patient is advised to face his phobia or when a compulsive patient is advised to desist from his compulsion. These measures, while acting through suggestion, are employed for the purpose of mobilizing anxiety in order to promote the treatment process. Emotional ployment differs from suggestion in that it uses emotional forces outside the transference situation (the ego and the superego), whereas suggestion operates within the transference situation (abrogation of the ego and the superego). In practice the various technical devices of psychotherapy overlap each other.

Nondirective therapy is mainly an emotional reployment of the patient's feeling accepted and gradually gaining in self-reliance and independence. To this is added what Rogers [15] has called *clarification*. This is a technique of psychotherapy which consists of restating in more precise form the patterns and feelings which accompany the patient's main trains of thought. Clarification seeks out the common denominators in feelings, attitudes, perceptions, thoughts, impulses, character traits, and reaction patterns. The explanation of these denominators are interpretations on a conscious and preconscious level which were introduced into psychoanalytic technique by Sigmund Freud, Anna Freud, Wilhelm Reich, and others who focused on the ego. Nonanalytic psychologists, whose main arena has always been the ego, borrowed this technique, and Rogers gave it the name "clarification." In treatment by psychoanalysis, clarification is a preliminary step to interpretation of the unconscious. It is clarifying to the patient to point out those instances in which he displays feelings of inferiority. It would be an interpretation to link these feelings of inferiority to his childhood feelings of inadequacy in comparison with his father in a fantasied sexual situation (i. e., Oedipus complex). Similarly, dependency feelings on the part of a patient may be clarified for him by showing various situations where they occur. Interpretation would show how the dependency on the analyst repeats too closely, and hence inappropriately, the dependency on the mother at an early stage in childhood.

Clarification aims at self-understanding, but not at finding out the origin or mode of development of the particular pattern. It seeks to promote in the patient a detachment of the ego through more differentiated self-awareness, which favors a better control of behavior through a more realistic knowledge of himself and his environment. Through clarification, the patient develops the capacity for objective self-observation ("immanent objectivity" of Hollingworth).

The following case illustrates the technique of clarification:

CASE 6.—A 20-year-old woman, in her third year at college, was referred for treatment because of severe acute depression. Although a good student and a member of the "best" sorority, she felt increasingly ashamed of herself and became obsessed with the ideas that she did not "belong" and that she was not good enough. This state of affairs had resulted from the fact that she found herself at ease only on those dates where the boy seemed to be not quite up to her standards; she became anxious and managed somehow to antagonize him. Several such experiences resulted in her having fewer and fewer dates, and she began to feel that she was friendless. It came as a revelation to the patient when it was clarified for her that her feelings of inferiority had brought about the state of being without dates rather than the reverse. It was clarified for her that her emphasis on the "best" school, the "best" sorority, the "best" boys were all aspects of the need to be "best." Her emphasis on appearances, of which she was aware only peripherally (preconsciously), was clarified for her. The groundlessness of her fear of changing schools was clarified for her once she saw that she was over concerned with appearances. Later, when she had graduated from a college near her home (to which she had trans-

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Development of an Active Therapeutic Program on a Chronic Ward

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In recent years there have been many efforts to alter traditionally custodial psychiatric hospitals into more psychotherapeutic rehabilitative organizations. The project herein reported was undertaken to transform a chronic custodial psychiatric ward into one that actively encouraged and supported patient improvement and rehabilitation. As one of several projects initiated to improve patient care in a large state hospital, it was begun shortly after a similar program had been instituted on another ward in the same building. The personnel from both wards met weekly to discuss problems encountered on their respective units, and the over-all approach was evolved in these meetings and personnel conferences on each ward. As is the case in most state hospitals, there were limitations in the number of personnel and amount of money available to carry out the program.

This paper is written to describe the evolutionary process on one ward from October, 1956, to October, 1957. An effort has been made to record most of the factors involved, and these are commented upon. However, there is room for additional speculation about all of the forces that come into operation as a project such as this gets under way, gathers momentum, and changes begin to take place.

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Dr. Anthony Velez, Resident, Chicago State Hospital, was diligent in his assistance in this work. Dr. Kalman Gyarfas, Superintendent, Chicago State Hospital, gave permission for and cooperated in this study.

Conditions Existing in the Beginning, October, 1956

This ward is one of eight similar ones in a four-story building, containing approximately 1500 female patients. The dining room is attached to the rear of the first floor, and all patients use stairways to reach each level. The ward being described is on the third floor and consists primarily of three large rooms, approximately 50 × 150 ft. each. Between the centrally located dayroom and each of the two dormitory rooms are storage, bathing, and toilet facilities. There are 75 beds in each dormitory, and at the outset of this project there were approximately 185 patients on the ward, so that about 35 were sleeping at night on cots in the dayroom. One of the dormitory rooms was designated as the "untidy" room, where all patients incontinent of urine and feces slept. The mattresses and bedclothing in this room were consistently foul-smelling. This ward was known as the "worst" in the entire building, and all patients on it were considered to be hopeless and deteriorated. As a matter of fact, it was not uncommon for personnel to make statements to this effect in the presence of patients.

Patient activities were largely restricted to approximately 10 "working" patients, who carried out many of the ward chores, such as making beds, sorting linens and clothes, helping attendants give baths, and cleaning up incontinent patients. Patients who worked were given privileges in the form of special food and orders from the hospital commissary. The rest of the patients slept, ate three meals a day, occasionally watched television, or listened to the

radio; but most frequently they sat quietly on the floor or the benches or rocked in the rocking chairs. Frequently they would be masturbating or performing bizarre movements. Intact plain clothing was issued to them periodically, but many insisted on tearing up these clothes and going around partially nude, disheveled, and barefooted. The interactions of these very regressed patients consisted largely of verbally or physically attacking each other. Several working patients spent their time in a special dayroom area cleaning up behind patients who were incontinent of urine and feces.

Most of the patients had been hospitalized for over 10 years; some of them for over 25. Chlorpromazine had been in use on the ward for over a year and was being used to calm excited, hyperactive patients. It was being given on a p. r. n. basis by the attendants, and many patients were somnolent from excessive doses. There was no way that an efficient record of drugs administered could be kept. Smoking was not allowed in the dayroom, dormitory rooms, or dining room but was allowed in the crowded washrooms, where the toilets and lavatories were located. There the odor of urine and feces was strong because the toilets frequently were not flushed and also because some patients defecated and urinated on the floor. There was no place where a patient could keep her clothes and possessions in an orderly fashion and safe from other patients; some had individual shopping bags or purses in which they kept small personal objects. In general the appearance of the patient group was one of tattered, torn clothes on dejected, forlorn-looking persons. There was a high incidence of pyoderma, and scabies was common. Many patients had edema of their legs and ankles. Some of the women wore only a torn dress; and since many of them were overweight, they were uncomfortable without proper supportive undergarments.

There was a minimum number of personnel on the ward at all times. Usually a physician visited for a few minutes each day to examine and treat physically ill patients. Problem patients were most often handled by transfer to other wards.

Supervisory nurses spent several hours a day helping care for patients and overseeing the maintenance of cleanliness on the ward. The personnel consisted mainly of attendants with a high-school level of education and a short course of psychiatric training before starting to work on the ward. Some of them had worked on this ward or in the hospital for 10 years or more. They wanted to help the patients, but they seemed to be frustrated and discouraged. Occasionally there would be only one attendant for an eight-hour shift, although it was felt that for safety there should be at least two, because the patients at times were physically assaultive. On the day shift there were occasionally three, and rarely four, attendants on duty. The number was always insufficient to give more than minimal care to patients or keep any kind of records.

Changes Introduced

In the introduction of initial changes, personnel members were informed about the general program and were given an opportunity to express their ideas. They could express their thoughts and feelings in patient group meetings, as well as in separate meetings. The entire staff gave encouragement, stimulation, and support to each other in their joint and individual efforts.

An important step in introducing the therapeutic milieu was helping patients understand that they could participate in conducting ward activities through group meetings, which were to be conducted for an hour a day five days a week. The psychiatrist and psychologist explained repeatedly to patients individually and in the group that they could express their feelings, problems, and requests. The meetings were to be a forum where patients could interact, discuss their problems with each other, and learn that someone would respect their opinions. This was an opportunity for each

patient to rebuild her self-respect and be accepted as a person in her own right.

By means of discussion and voting, the group could grant passes to go onto the hospital grounds, passes to leave the hospital grounds, and discharges from the hospital. Passes and discharges were no longer to be dispensed by the physician or attendants. Group decisions were to be honored except when the decision was obviously not reality-oriented. When this occurred, it was the perogative of either therapist to veto and initiate a group discussion to determine the cause of the unrealistic decision. To obtain a grounds pass, for example, a patient requested it in the group. It was discussed whether or not the person's behavior was socially acceptable and would not bring discredit on the group. The patient was given a pass signed by the psychiatrist if approved by group vote. If a patient requested a discharge, she was asked to have a member of her family attend a meeting and discuss plans that had been made to help her adjust after leaving the hospital. Criteria for discharge were based on considering each patient in terms of the unique life situation into which she would go upon leaving the hospital instead of whether or not she was asymptomatic. It was in this frame of reference that the group was guided by the therapists in discussing requested discharges.

The project was also mobilized by the introduction of group and individual occupational therapy. There was one occupational therapist who was occasionally helped by two or three volunteer workers. They offered the patients an opportunity to sew, iron, knit, plan parties, or do handicrafts. Initially the projects took place exclusively on the ward, but as interest in these activities increased, patients began to go to the occupational therapy building on the hospital grounds. The new recreational therapist conducted group singing and dancing, group walks, and planned trips to places of interest, like the zoo. These two types of therapy were designed to build self-confidence and self-esteem by helping patients do things for themselves.

Another change effected was in the use of industrial therapy. There were a number of jobs available on the hospital campus and the ward. It was emphasized that these jobs were not compulsory; anyone could quit at any time, and was to work only if she wanted to do so. The purpose was to help patients get used to working; however, hospital personnel tended to regard the jobs as a hospital service instead of a therapeutic activity. It was also possible for a patient to get a job outside the hospital but continue to live on the ward until she had saved enough money to move out to a residence of her own.

In addition, the social service department was available to help patients plan to leave the hospital, get jobs, contact relatives, or locate a place in which to live. Simultaneously with the above-mentioned changes, the ward patient population was altered gradually by admitting acutely ill patients to the ward, but not transferring older patients unless necessary because of physical illness. The changes were gradual to minimize disruption of any stability that was already present in the patient group.

Approximately 40% of all patients were incontinent of urine and feces at the outset of the project. An effort was being made to keep them confined in one section of the day room, where several working patients were stationed with mops and necessary equipment to clean up. Their soiled bedding and mattresses were periodically discarded when they were judged to be completely ruined. The first step to overcome this problem was to do away with the special area in the dayroom. The attendants and some patients began to encourage and guide the incontinent patients to the toilet at intervals during the day. In the group meetings the foul odors and unpleasant appearance of the incontinent patients were complained about, and on several occasions a group of them was asked to come to the meeting. The therapists stated explicitly to this group

that they did not have to neglect and depreciate themselves by being incontinent. They were encouraged to make their own lives more pleasant by using the toilet facilities. Each step of this process brought a decrease in the size of the incontinent group.

The Group Meetings

The group meetings, which originally were made up of 10 or 12 patients and personnel sitting around a table, evolved into a meeting of approximately 25 or 30 people, who sat in a circle in the dayroom. Other patients stood around or sat in chairs beyond this central group, and some seemed to be active participants, though they sat as far as 20 ft. from the group. It was not uncommon for a patient outside the group area to shout or hold up her hand or attack another patient or cause some sort of disturbance that would focus the attention of everyone on her. She would be asked by a therapist if she wished to say something in the group, and usually she joined the group and would participate. Sometimes the patient could be understood, but at other times the material verbalized was extremely psychotic and all that could be done was encourage her to make herself more easily understood, thereby expressing the interest and the willingness to listen of the therapists and the group. To deter demonstrative or destructive behavior, it was frequently reiterated that it was unnecessary to cause a disturbance in order to join the group meeting; they could simply come and talk without other activity. At times the group would become chaotic, with almost everyone talking at once. On such occasions it was necessary for one of the therapists to call for silence and insist that they show each other the respect of listening to one person at a time.

There was a feeling among personnel that patients should be required to come to the group meetings because this was the only form of therapy available to the majority of them. Only a few patients (three or four) were in individual psychotherapy with other psychiatrists. If patients requested that they be allowed to leave the ward during a meeting, the group therapists would grant this privilege after a discussion of the reasons for leaving.

The general attitude of the therapists was to be supportive to the group and to the individuals in the group. They actively encouraged the patients to make decisions and work together. The therapists wanted to avoid being authoritarian or dominating in the group situation; however, patients sought constantly to put them into this position. For example, a patient would quite often come and stand immediately in front of the therapists and talk; at such times she was asked to return to her seat or at least take some position where the group as a whole could be included in what she had to say. It was not uncommon for a patient to say: "Well, you are the doctor, and it is up to you to make a decision about this matter." At this point a therapist would point out the responsibility and privilege of the group in making decisions for patients to abide by. There were times when a patient was successful in persuading a therapist to circumvent the group process by granting a grounds pass or a home-visit pass without the consent or discussion of the group. These privileges were frequently unsuccessful and unsatisfactory. It seemed as if the patient had been able to make the therapist authoritarian, and therefore responsible for her actions, and on this basis inappropriate behavior occurred. The repeated reply to requests was: "Bring this up and discuss it in the group."

On some occasions one patient would talk for the entire hour about her emotional problems, and at these times the primary function of the therapists was to be quiet so that patients could listen and give their views to the person speaking. If silence persisted in the group, however, the therapist would ask if any one else had had an experience similar to that being described, for instance, a nervous breakdown, hallucinations, delusions, fear of dying, etc. This

often stimulated members of the group to compare notes, and they would be surprised to find a number of other people with similar problems. If a patient talked about something that seemed very significant, a therapist might ask her to repeat what she had said so that more people on the fringe of the group could hear it. Patients were frequently encouraging and supporting to each other.

Interpretations were made by a therapist on some occasions; most of these were oriented in the frame of reference that each person has a right to live and have some gratifications. The group itself could furnish some gratification in the form of passes and discharges. Each individual patient had to request her own privileges and thereby demonstrate that she felt entitled to them. The group rejected a request by a patient only when that patient seemed unwilling to do her part in assuming responsibility for what she asked. For example, a woman who would not dress properly, would not wear shoes, and frequently exposed her body was not given a grounds pass by the group members because they said she was not able to maintain an appropriate appearance. This patient subsequently promised that she would improve her appearance, which she did, and the group granted her a pass to leave the ward.

Because there were many gradations of psychosis manifested by this large group, some of the patients on a better level considered themselves well and other patients sick. The more deteriorated, regressed, and withdrawn women were referred to as being "crazy—they do not know anything—they are hopeless—what is the use of listening to those crazy people talk in the group?" At this point the therapists would reiterate the fact that these more disturbed patients do know what is going on around them and do have a capacity to understand. It was repeatedly stated that some people require years to work out their problems sufficiently to be discharged from the hospital or have grounds passes or other privileges. Each person was told that she had the same opportunity as anyone else on the ward to have privileges or receive a discharge if she made an effort to do so.

If there were conflicts between individual patients or between patients and personnel, or if there were factors in the living conditions on the ward, such as rules or regulations, which the patients felt should be changed, these matters could be discussed and voted on. On one occasion the patients requested the same bedtime hour as other wards in the hospital. This was discussed and voted on, and the ward nursing supervisor served as liaison with the administration and the change was made. At times a dispute arose between patients on this and another ward; so a patient committee was formed to visit the other ward to attempt a solution of the problem. This was done, with varying success. On another occasion the patients felt better clothing would help them feel better; so a committee was formed to talk to the clothing management of the hospital. On this occasion one therapist went to the clothing department and made sure that the people there were willing to talk to the patients and give realistic consideration to their requests. The primary importance of this action was realization that patients could form committees and discuss matters with administration officials.

It was emphasized that patients were free to make their individual decisions. Some patients who had been working on the same ward job for years decided to quit; they sought reassurance about this, and it was given. This type of action at times upset the equilibrium of the ward personnel; however, they were able to adjust to the situation, and it seemed a healthy step for the patients. The special rewards that had been given working patients were discontinued, because each patient was to be treated equally, so that their work would be on a voluntary basis. Patients were invited to explain to the group how they felt that working had helped them and the group, as it was obvious that personal-work ac-

complishments were a major source of increased self-esteem.

Occasionally, only six or eight times in the whole year, the group would make decisions which were questionable. One incident concerned giving grounds passes to a manic patient who was extremely provocative, loud, and irritating to every one with whom she came in contact. After revoking a grounds pass for her inappropriate activity off the ward, the group decided to give her another. The decision was obviously a poor one and was vetoed by a therapist. At this point the patients stated they felt she should be given a grounds pass to get rid of her because she was bothering them. This was taken as an indication to transfer the patient to the small hydrotherapy unit, where she later reintegrated and was discharged when she returned to the ward and requested it in the group. Such transfers were discussed in the group, and the hydrotherapy unit lost much of the terror attributed to it by the misinformed patients.

There were times when it was felt that individual patients needed special emotional support. For example, when someone expressed strongly emotional material in the group, other patients would often react to this. This was pointed out when they sought to interrupt; and the group was reassured that it was useful to express such affect. If a patient became quite upset, she would be reassured after the meeting by a therapist and encouraged to stay on the ward until she felt calmer. At such times the attendants also gave special attention to the patient.

When relatives would attend group meetings, they were always asked if they would like to participate, and often they did. They were frequently surprised that patients could talk coherently and discuss problems with a realistic approach. Occasionally a relative would place a great deal of pressure on a patient to ask for a discharge. It was difficult at times to ascertain whether the patient actually wanted to go home with the relative. Discharges for which the request had come from the relative instead of the patient were frequently unsuccessful and of short duration. Severe interpersonal difficulties seemed to occur more frequently under these conditions.

Difficulties Encountered

The greatest difficulty was altering attitudes of traditional personnel members who had worked there for varying lengths of time, many over 5 years and some longer than 10 years. The general attitude toward patients was that they were hopeless, dumb, stupid, deteriorated, and did not know what was going on. "The patients do not want more; why give to them or try to force them to have things?" seemed to be expressed. In the past, if a patient had become active and protested in any way, she had customarily been labeled "bad" and given large doses of chlorpromazine (Thorazine), hydrotherapy, or, in some cases, electroshock therapy. The electroshock therapy had been prescribed by a physician who spent a brief time on the ward daily. The custodial attitudes of the nurses and attendants permeated the entire hospital, and the training program was predominantly concerned with techniques of controlling patients. One attendant expressed her defeatist attitude by saying: "After all, doctor, I have been here for five years and have not been able to get these people well. How do you expect to do anything with them?" The biggest problem was to help personnel understand that patients are people who have human needs for love, care, and consideration.

There were many realistic practical problems. For example, on the ward with 190 patients, it was not uncommon to have only one or two attendants on duty. Occasionally there was a physically assaultive patient who threatened to harm the attendants; so there was realistic fear to consider. Also, the facilities for patient care were markedly overtaxed; there was frequently a shortage of linen, soap, towels, toilet paper, clothes, and personal storage space for each patient. As has been related earlier, bed space was

limited; so cots had to be used in the dayroom. An authoritarian suppressing system had seemed to be the only way that so many patients could be cared for by so few attendants. Often there was a substitute attendant who had never worked on the ward, and this upset routine patient care. It was common knowledge that some attendants would leave the hospital feigning illness if they were assigned temporary work on this ward, because it had such a bad reputation. The pessimistic attitudes of ward attendants were amplified by the patients' demonstrations and verbalizations of their own feelings of hopelessness. These were feelings which the patients eventually began to express in the group meetings.

There was one strong positive asset, however. Among the majority of personnel there was a willingness to be shown that patients could get well or at least improve themselves and the living conditions of the ward. Many attendants seemed to understand intuitively that the patients could somehow improve, and they showed a genuine interest in promoting this improvement. Some attendants could work more effectively with certain patients than others. Individual staff-patient relationships were encouraged and discussed among personnel members at staff meetings. As progress began to be manifest on the ward, there was pride and pleasure on the part of the personnel in knowing that they had been a major factor in helping to effect the changes. At one point the patients voted for and obtained the transfer of one aide who they felt was uninterested in them or in the program.

Occasional difficulties arose when physicians who were unfamiliar with the ward program assumed administrative responsibilities overnight and weekends. They were prone to transfer patients arbitrarily or use sedation excessively. To avoid this, an attempt was made to inform all hospital physicians about the nature of the program. This met with varying degrees of cooperation.

Among supervisory nurses, attitudes varied from wholehearted cooperation to passive resistance to overt rebellion against the proposed changes. Some nurses who had been working at the hospital for a long time were adamant in their conviction that patients were not entitled to participate in the conduct or policy making of the ward. By and large, however, as progress was made, the nurses became more positive in their attitudes and actions. Those who did not, seemed to feel threatened with a loss of personal prestige and authoritarian power.

One problem in maintaining ward stability was the rotation of psychiatrists: The first was there six months; the next three months, and the third three months. Fortunately, the ward psychologist was present for the entire time and gave the group meetings a sense of continuity when the psychiatrist was replaced. The stability was also maintained through the continued efforts of nurses, attendants, and the occupational and recreational therapists, all of whom had individual relationships with patients. These relationships were definitely therapeutic in many instances.

Results

Results of the program were observable within three months, and at the end of a year changes were marked. There was much more verbal interaction among patients and between patients and personnel. There was a great increase in the constructive occupational and the recreational therapy. The cleanliness, neatness, and grooming of the patients were improved. There was much less destruction of clothing. Incontinence of urine or feces in the dayroom had become a rarity. The ward appearance was enhanced by potted plants and decorations, which a year previously would probably have been destroyed. In the dormitory rooms there was no odor of urine or feces; the beds were cleaner and had a better appearance. In the bathrooms there was much less odor, because the toilets were being used properly. In the

bathroom area where smoking was permitted, there were new benches and chairs where patients could sit and talk while smoking, instead of having to stand or sit on the floor, as had been the case previously. There was a marked decrease in the number of patients who stayed on the ward during the day; so those who remained received more attention from personnel. When the program began, only five people had grounds passes. At the end of a year this number was approximately 70. No patient had been allowed to leave the hospital grounds unattended previously, but at the end of the year there were approximately 20 people who had this privilege.

Whereas a year previous there were approximately 185 patients on the ward, the number had increased to about 195. This increase had occurred because new, relatively acute patients had been admitted to the ward. This mixing of acute and chronic patients seemed to have several interesting effects. The initial reaction of many acute patients was to say: "I certainly do not want to become like those chronic patients. I want to get well and go home." This was a strong motivating factor to make a genuine effort to seek discharge. Also acute patients in many instances interacted with and stimulated chronic patients to improve their appearance, and the living conditions on the ward, and request off-unit and off-grounds privileges. A chronic patient 30 ft. from the group one day asked: "Can only new patients get discharged from here?" This was an opportunity in the group situation to reemphasize that it was possible for any patient to receive a discharge if she requested it and made realistic plans to leave. In the group meetings acute patients, who were generally more verbal, encouraged chronic patients to talk and express themselves. In some instances acute patients formed relationships with long-term patients to the extent that they would visit off the hospital grounds together with a feeling of mutual support. In the group meetings a relatively small number of patients did most of the talking. For example, in a group of 35 patients, 5 to 10 led the discussions, and the others made only occasional comments. As members of this group of 5 to 10 were discharged, some of the older chronic patients became more active; also in ward occupational-therapy activities, as the group became smaller because of patient off-unit privileges, an older group of patients began to participate.

The patient's relatives were quite impressed with the changes on the ward. It became a pleasanter place for visiting, and this helped increase the number of visitors. Patients were encouraged to write to relatives and friends if they had any. Staff members of the hospital visiting the ward expressed pleasure at the progress, and this was encouraging to the patients. There was also interest verbalized by patients in other parts of the hospital when they heard about the project. The relatives and visiting members of the hospital staff were often surprised to hear patients discuss problems with clarity, intelligence, and good judgment; and they were just as impressed to see that patients who spoke in a psychotic bizarre manner were not rejected by the group. In fact, these patients seemed to respond positively to the fact that they were not rejected. Throughout the hospital the ward gradually lost much of its reputation for being such a terrible, hopeless unit.

As patients began to have the privilege of going off the grounds alone, they began to seek jobs outside. Several worked outside and stayed in the hospital a few more weeks until they had sufficient funds to obtain a private residence. Patients who were discharged were encouraged to seek either private psychiatric help or state-sponsored group or individual therapy; those who wished to return to ward meetings were always welcome. It was encouraging for patients on the ward to have someone visit and state that she had been able to "make a go of it" on the outside.

and also talk about some of the problems she had encountered.

The effects of the total ward changes on personnel were generally positive, particularly the attendants who were with the patients for eight hours a day. They were encouraged and gratified by the results and developed increasingly therapeutic attitudes. The feeling was that the total program was an effective means of helping each patient. This, in turn, promoted healthier interactions between patients and personnel and the general atmosphere became friendlier and more cheerful. However, if there was discord between patients and personnel, everyone knew that they could express these feelings in a group meeting without censor. This was done many times and relieved many episodes of tension.

Comment

At this point it is worth while to attempt to formulate a broad, inclusive concept underlying this project and its multiple facets. In the practice of medicine, treatment is designed to help the sick person overcome the disease, and psychiatric illness should be no exception. The hospitalized schizophrenic patient does not need a suppressing, controlling form of care. The illness consists of an elaborate internalized system of extreme self-suppression, including severe self-depreciation, self-deprivation, and self-punishment. If these patients are to be helped to free themselves of their extremely constricting and isolating condition, they must be given every opportunity to express themselves, seek gratification, rebuild their self-respect, and establish for themselves a place in the world. All efforts reported in this study are oriented in this direction.

Healthy, mutually beneficial interpersonal activity was fostered, and exploitative, bullying, mutually destructive activity was pointed out and frankly discouraged. Free verbalization and communication of wishes, likes, and dislikes were the order of the day. Dissatisfactions were opened up and aired out, instead of being glossed over. Communication channels were available to all levels of the hospital staff and administration through patient-committee action. Decision making was a democratic group process in which each patient was encouraged to use her individual judgment and express her opinion. Individual patient motivation was nurtured whenever it was manifest. Patient interrelationships became supportive in nature when there was communication between patients and mutual problems were recognized.

Theoretically speaking, it is easy to delineate "the patient group" and "the personnel group." This is as far as it goes, however, because all of the people involved, patients and personnel, made up a large, multidimensional, constantly interacting group of people. Actions and reactions reached all levels of the staff, and a "snowballing" effect was quite often evident because of the interrelatedness of changes, whether toward a therapeutic constructive atmosphere or just the opposite. So, in the final analysis, it can be said that if we have correctly diagnosed and appraised the disease, we have made progress in the general direction of treating it properly.

It is worth while to compare the present study with representative projects having similar goals. In the work by Cumming et al.[1] there was an attempt to promote a high level of interaction among patients and personnel and between these two groups. This was done by reorganizing the total hospital staff structure to facilitate communication at all levels and by using norm bearers to disseminate and encourage therapeutic attitudes and techniques among the personnel.

The approach used by Miller and Clancy[2] in working with chronic schizophrenic patients was to use a "permissive push." A wide range of cultural environmental manipulation was accomplished by elaborate occupational and recreational therapy activities. The purpose was to improve

the social performance of the patients by means of group activities.

At Boston Psychopathic Hospital the patient government[3] was established on the initiative of patients who were apparently on a somewhat better level of integration than patients reported in our study. In the Boston study a permissive atmosphere, freedom of expression, and self-determinism were encouraged by permitting the patients to discuss and carry out projects initiated by themselves. One difficulty experienced by personnel in this system was their tendency to assume an authoritarian role, and this pitfall was noted in our study.

The beneficial effects of patient interrelationships in promoting recovery from psychiatric illness have been noted by Bartemeier[4] and others. Other approaches, including intensive efforts to explore primary process thinking and psychotic processes,[5] have been used in an effort to generate a therapeutic milieu.

Summary and Conclusion

This paper concerns a 12-month period devoted to developing a ward program which encouraged chronic hospitalized psychiatric patients to rebuild their self-respect and seek gratification by expressing their feelings and wishes and interacting with each other. The communication center was daily group meetings where the democratic process was instituted. The patients, under the guidance of therapists, could initiate ward projects and discuss ward problems. The group listened to individual patient problems and granted patient privileges by vote. This furnished opportunity and emotional support for each patient to improve her life situation by using her own motivation. The therapists had the right to veto unrealistic decisions and help the group determine sources of error. This was necessary only six or eight times in the 12-month period. The therapists gave support and interpretations to individual patients who spoke of problems in the group or in individual contacts. There was no electroshock or insulin therapy used, and there was a decrease in the need for chlorpromazine (Thorazine), hydrotherapy, and other restraining forms of therapy. Very few patients were allowed to be transferred off the ward unless physically ill because of the implications of rejecting anyone in the group. When patients were discharged, it was felt that they should be replaced with acute patients because of the stimulating effect of the latter on the ward program. Many practical problems arose because a larger personnel and more equipment were needed. Experienced, custodially oriented personnel can develop more psychotherapeutic rehabilitative attitudes.

In a permissive, nonthreatening, encouraging, democratic atmosphere, chronic psychotic patients will seek gratification and make efforts to rebuild their self-confidence and self-respect. Many of them will not seek discharge because they have no place to go; however, for those who stay in the hospital indefinitely, their living conditions can be greatly improved. They can to some extent come out of their self-imposed isolation, relate to other patients like themselves, and gain some mutual gratification. They can reach some understanding of themselves and other patients, personnel, and relatives. The relatives can gain some understanding with patients. It is certainly less anxiety- and guilt-provoking to visit a relative on a ward that is clean and pleasant than on one where the appearance and odor of urine and feces is commonplace, the people wear their clothes torn to shreds, and the atmosphere is one of complete hopelessness and frustration. Likewise, the personnel members who work on such a ward are better able to help patients when conditions are favorable and pleasant and they are not constantly threatened with physical violence, so that they feel a need to control and restrain the patients. An approach to individual freedom for patients has been made by their having the oppor-

tunity to set their own limits and pursue achievement by their own action.[6]

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Mechanisms Involved in the Cardiovascular Response to Transcranial Stimulation

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In patients undergoing electroconvulsive therapy (ECT) an intense circulatory reaction takes place, which includes marked changes in arterial pressure (Silfverskiöld and Amark[1]; Holmberg et al.[2]; Richardson et al.[3]) and cardiac rate and rhythm (Bellet, Kershbaum, and Furst[4]; Bankhead, Torrens, and Harris[5]; Green and Woods[6]). These cardiovascular effects are of considerable practical importance, since circulatory strain is reported to be the leading cause of death in electroconvulsive therapy (Maclay[7]; L. Alexander[7]; S. P. Alexander, Gahagan, and Lewis[10]; Lewis[11]; Impastato[9]).

The typical cardiovascular response to ECT is diphasic. Immediately after the stimulus a sharp, but short-lasting, fall in arterial pressure occurs, accompanied by bradycardia or, in some cases, by asystole, of several seconds' duration. This is followed by a phase of acute arterial hypertension, which persists for five minutes or more. Tachycardia is prominent during the hypertensive phase. The general pattern of response has been demonstrated by Brown et al. to be similar in the human,[12] dog,[13] and monkey.[14]

The initial cardiac slowing during ECT can be eliminated by premedication with atropine (Bellet, Kershbaum, and Furst[4]), suggesting that this phenomenon is mediated through the vagus. Lewis et al.[15] classified the arrhythmias occurring in ECT as vagal or extravagal, depending upon the ability of atropine to prevent the cardiac slowing or arrest; any arrhythmia developing after full atropinization was classified as extravagal. These authors recorded extravagal arrhythmias in over 50% of the treatments in one series of patients. The series contained a disproportionately large number of patients with preexisting cardiovascular disease; the results, however, serve to emphasize the ever-present danger of ventricular arrhythmias occurring during therapy.

The present series of experiments were designed to clarify the characteristics of the cardiovascular response by a study of (1) the cardiovascular changes and (2) the basic mechanisms involved.

There is an obvious resemblance between the response to ECT and that observed with certain types of autonomic activation; typically, bradycardia and hypotension are cholinergic, and tachycardia and hypertension adrenergic, cardiovascular effects. In addition to the preventive effect of atropine against the cardiac slowing of the initial phase, evidence of parasympathetic participation is provided in the animal studies of several different investigators which demonstrate that bilateral vagotomy eliminates the bradycardia and blood pressure fall that follow the transcranial application of an electrical current (Ivy and Barry[16]; Frostig et al.[17]; Brown, Brown, and Hines[13]).

Weil-Malherbe[18] has reviewed the evidence pointing to the activation of the sympathetic nervous system after ECT or analogous procedures in animals. In this

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same communication, the author presents material showing a rise in plasma epinephrine and arterenol (norepinephrine) following this type of treatment. This finding has recently been confirmed by Manger et al.[19] insofar as epinephrine is concerned; blood levels of arterenol, however, were found to be elevated in only 5 of the 12 patients studied by this group. Also indicative of adrenergic participation in the cardiovascular response is the observation by Richardson et al.[3] that the administration of the ganglionic-blocking drug tetraethylammonium chloride (TEA) prior to ECT partially blocked the hypertensive response.

Method

A total of 25 male or female dogs were anesthetized with pentobarbital (30 mg/kg) intraperitoneally. All other drugs were administered by a catheter inserted in the femoral vein. A one-second sinusoidal stimulus of 150 volts was applied transcranially by means of a Medcraft Model B-24 ECT unit. The two temporal electrodes were fastened to the dog's head with bandage, electrode jelly being used to ensure proper contact. As reported by Ellis and Colville,[20] the 150-volt one-second stimulus under these conditions is always supramaximal in terms of the production of the cardiovascular response. We have termed this procedure transcranial stimulation or TCS.

It was found that after each stimulation the arterial pressure returned to control levels before 15 minutes had elapsed and that succeeding stimuli evoked reproducible vasomotor responses. Effects of drugs and surgical procedure, therefore, were determined by comparing the control response with the response obtained 15 minutes later; drugs were given or surgery performed during the 15-minute interval. An exception was adrenalectomy, where approximately 40 minutes separated the control and post-treatment response.

Succinylcholine (Anectine) chloride was administered prior to each stimulation to eliminate any cardiovascular changes due to muscular contraction; artificial respiration was supplied with a Palmer Ideal pump.

A Sanborn Polyviso was used for recording. Blood pressure was registered routinely from a cannulated carotid artery connected to a Statham transducer. Electrocardiograms (Lead II) were recorded from 15 of the 25 dogs.

In order to discriminate between the effects of TCS on the heart and those on the blood vessels, animals were prepared with a Walton strain-gauge arch[21] sutured to the left ventricle to record the force of cardiac contraction and with a perfusion system for the hindlimb, using a Sigmamotor constant-flow pump. A cannula inserted into the cardiad portion of the femoral artery led blood to the pump, from which it was expelled at a constant rate into the distal portion of the artery. A Statham transducer connected to the perfusion line by polyethylene tubing enabled the recording of perfusion pressure, which was maintained during control periods at 125-150 mm. Hg. Since blood flow into the area was maintained at a constant rate by the pump, changes in perfusion pressure could be brought about only by dilatation or constriction of the vessels of the limb.

Results

Nature of the Response.—As shown in Figure 1, the heart ceases beating (usually for from four to seven beats) immediately after the stimulus. When the beat resumes, it is with a stronger contractile force, which gradually increases as the arterial pressure rises. Atropine completely eliminates the cardiac slowing and also enhances the force of ventricular contraction early in the pressor phase. The fall in arterial pressure coincides with the period of ventricular asystole and is similarly abolished by atropinization. The absence of tachycardia, shown in Figure 1, is typical of this series and marks the greatest point of difference between the present animal experiments and the clinical response, in which a marked tachycardia is almost invariably observed. The difference very likely is due to the greater depth of anesthesia used in these studies.

It was found that it took approximately 60 seconds for blood to flow through the perfusion system; consequently, no vasoactive substances liberated by the stimulus reached the limb during this interval. Changes in perfusion pressure occurring during this time, therefore, can be ascribed only to neurogenic mechanisms. No vasodilatation takes place in the limb during the period of greatest vagal discharge but does occur as the arterial pressure rises, and finally verges into vasoconstriction. The fact that vasodilatation coincides with

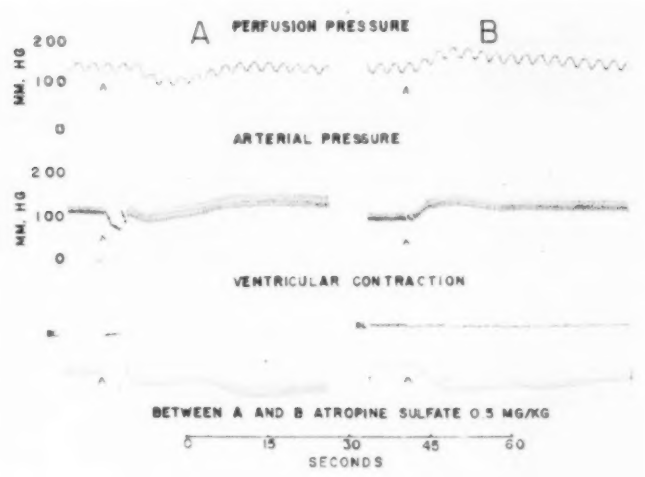

Fig. 1.—*Effect of transcranial stimulation (TCS) on hindlimb perfusion pressure, carotid arterial pressure, and ventricular contraction. TCS applied at arrows. An increase in cardiac contractile force is registered as a greater downward deflection of the writing pen from the base line, BL.*

the pressor rather than the depressor phase of the response suggests a sympathetic motivation. Burn [22] has demonstrated the existence of vasodilator fibers in the hindlimb of the dog which have anatomic connections with the sympathetic nervous system but which liberate acetylcholine at their terminals. The blocking effect of atropine in the present experiments is consistent with a sympathetic-dilator mechanism of this type.

After atropinization vasoconstriction in the limb is seen to occur immediately after the stimulus, as shown by the rise in perfusion pressure. Neurogenic vasoconstrictor mechanisms are thus demonstrated to be active, although masked in the unatropinized preparation, even during the period of vagal discharge.

Modification of the Response by Drugs and Surgical Procedures.—The Table lists the effect of certain drugs and surgical procedures on the hypotensive and hypertensive phases of the arterial pressure response to TCS. Since the point of greatest blood pressure fall after TCS occurs during the period of cardiac standstill, obviously no systolic measurements were possible during this period. Each value in the Table repre-

*Effect of Standard Drugs, Bilateral Adrenalectomy, and Spinal Cord Transection on the Arterial Pressure Response to Transcranial Stimulation.**

	TCS Control						TCS Post-Treatment			
	Hypotensive Phase, Mm. Hg Fall		Hypertensive Phase, Mm. Hg Rise		Fall Due to Treatment, Mm. Hg		Hypotensive Phase, Mm. Hg Fall		Hypertensive Phase, Mm. Hg Rise	
Treatment	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Atropine sulfate 0.036 mg./kg.	..	33	70	32	0	0	0	0	70	55
Atropine sulfate 0.5 mg./kg.	..	32	53	35	0	0	0	0	73	47
Tetraethylammonium chloride 6.0 mg./kg.	..	25	53	32	62	60	..	5	28	20
Hexamethonium chloride 10.0 mg./kg.	..	28	35	25	35	30	0	0	0	0
Bilateral adrenalectomy	..	27	57	30	40	40	..	25	18	20
Cord transection	..	27	82	52	20	23	..	25	0	0

* The measurements represent the fall or rise below or above the control arterial pressure level except for TCS post-treatment effects, which are measured from the treatment-induced level.

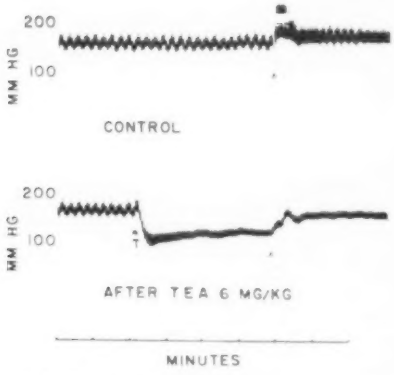

Fig. 2.—Effect of tetraethylammonium chloride, administered at *T*, on arterial pressure response to TCS applied four minutes later (at arrow).

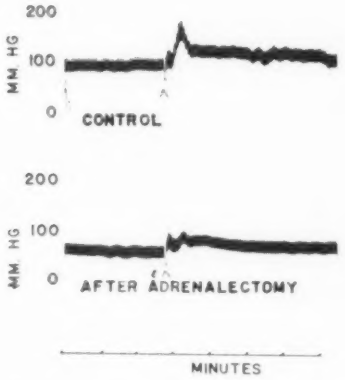

Fig. 3.—Arterial pressure response to TCS before and after acute bilateral adrenalectomy. Stimulus at arrows.

sents the average obtained from at least three separate experiments.

Atropine Sulfate: As little as 0.036 mg/kg. of atropine sulfate completely prevents the bradycardia and vasodepression following TCS. This or larger doses of atropine also cause enhancement of the following pressor phase (Table). In confirmation of the work of earlier workers, bilateral vagotomy was found to be fully as effective as atropine in abolishing the bradycardia and hypotension.

Ganglionic-Blocking Drugs: The experiments of Richardson et al.,[3] which demonstrate a partial blockade of the blood pressure rise during electroconvulsive therapy by a pretreatment injection of tetraethylammonium chloride (TEA), have been repeated in dogs and a comparable result has been obtained (Fig. 2 and Table). The initial vagal blood pressure fall is abolished by TEA, as would be anticipated, since drugs of this type block parasympathetic as well as sympathetic ganglia. Larger doses of more potent ganglionic-blocking drugs, e. g., hexamethonium chloride at 10 mg/kg., eliminate both the hypotensive and the hypertensive responses of the arterial pressure to transcranial stimulation (Table).

Release of Sympathetic Substances: Since an increase in circulating epinephrine and arterenol is known to follow electroconvulsive therapy,[19] it was of interest to determine what part the liberation of sympathetic materials from the adrenal medulla might play in the hypertensive response to TCS. Dogs were stimulated transcranially to obtain control responses and then were bilaterally adrenalectomized and the stimulus reapplied. A typical result of this procedure is shown in Figure 3. The rise in systolic arterial pressure after adrenalectomy averaged approximately one-third that obtained before adrenalectomy was performed (Table), the diastolic rise being affected to an appreciably slighter degree. This would imply that the liberated sympathetic substances exert a more pronounced effect in stimulating cardiac contractions than in constricting peripheral vessels. The residual hypertensive effect remaining after adrenalectomy would appear to be due to neurogenic mechanisms, i. e., caused by the release of neurohormone from sympathetic nerve endings directly at receptor sites in the heart and blood vessels.

Effect of Spinal Cord Transection: Since vagotomy was shown to prevent the cholinergic effects of TCS, it was decided to try the effect of the analogous procedure on the sympathetic nervous system, i. e., to interrupt it in its course from the central nervous system to the periphery by transection of the spinal cord above the level

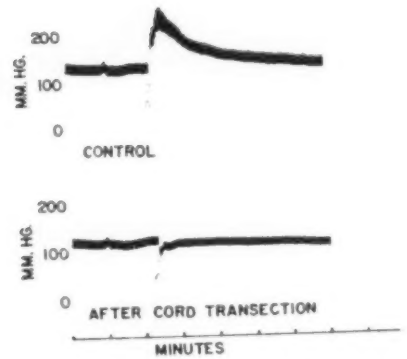

Fig. 4.—Disappearance of the pressor portion of the TCS response after section of the spinal cord at C-6. Stimulus at arrows.

of sympathetic outflow. The cord was exposed by removing the sixth cervical vertebra and, after control stimulations had been given, was cut at this site and TCS again administered. As shown in Figure 4 and the Table, the hypertensive response was abolished, whereas the initial blood pressure fall remained essentially unaffected. If the dogs with cords transected were then bilaterally vagotomized, no change in arterial pressure followed the application of TCS.

Arrhythmias: In dogs, as in man, vagal arrhythmias are of sinus origin and are characterized by cardiac slowing or arrest. In these experiments bradycardia invariably occurred unless blocking drugs were used or the vagi cut. Extravagal arrhythmias were encountered in 4 of 15 dogs, and ranged in severity from an occasional premature ventricular systole to brief periods of coupled premature systoles, and even short bouts of ventricular tachycardia.

In three of the four animals exhibiting extravagal arrhythmias, the severity and duration of the arrhythmia progressively decreased over the course of the first three stimulations (administered at 15-minute intervals), and were completely absent thereafter. A similar decrement in the hypertensive response on repeated stimulation was not observed in these animals.

Comment

The cardiovascular response to TCS appears to be the result of a generalized peripheral discharge of both branches of the autonomic nervous system. The cholinergic effects, bradycardia and hypotension, predominate during the first phase of the response; however, the use of atropine demonstrates that sympathetic vasoconstriction and cardiac stimulation also occur during this period but are masked by the overwhelming cholinergic reaction. The effect of vagotomy and cord transection would appear to show that the origin of the response is in brain centers, which, upon activation by the electrical stimulus, initiate trains of impulses which are conducted peripherally through the parasympathetic and sympathetic nervous systems.

The lessening in severity of extravagal arrhythmias upon repeated stimulation in three of the four animals in which this type of activity was noted deserves further investigation. Such a phenomenon is suggestive of the depletion of some substance necessary to the reaction. Whether this substance is epinephrine or epinephrine-like it is not possible to say at this time. The fact that the pressor response to TCS did not decline with repeated stimulation in these animals would imply that epinephrine is not greatly depleted.

Summary

The cardiovascular response to transcranial stimulation (TCS) under these experimental conditions consists of an initial hypotensive phase, caused largely by an intense bradycardia, followed by a hypertensive phase, involving both increased cardiac contractile force and peripheral vasoconstriction. The first phase is predominantly cholinergic; the hypotension and bradycardia are both prevented by the administration of atropine or by vagotomy. The second (hypertensive) phase is predominantly adrenergic; it is eliminated by section of the spinal cord above the level of sympathetic outflow.

Atropine, in addition to blocking the cardiac slowing and blood pressure fall, also causes an enhancement of the pressor portion of the response. Ganglionic-blocking drugs in sufficiently high dosage block both the hypotensive and the hypertensive reactions to TCS.

After bilateral adrenalectomy, the rise in blood pressure following TCS is considerably less, demonstrating the importance of circulating sympathetic substances liberated from the adrenal medulla in the pressor response.

Wellcome Research Laboratories (7).

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Effect of Anticholinergic Agent, Diethazine, on EEG and Behavior

Significance for Theory of Convulsive Therapy

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Recent investigations of convulsive therapy have emphasized EEG delta activity as the neurophysiologic basis for the induced behavioral change.[1-5] Little study, however, has been given to the biochemical effects of this therapy, except in the course of investigations of head injuries.

In investigations of head trauma significance has been ascribed to changes in the acetylcholine-cholinesterase systems both for the behavioral and for the electroencephalographic effects. An increase in free acetylcholine[6] and an alteration of the ratio of cholinesterases[7] in the spinal fluid have been positively correlated with the degree of EEG abnormality and degree of neurologic deficit. The EEG patterns were "blocked," and some improvement in clinical status was reported following the administration of atropine.[7,8] In convulsive therapy, atropine and scopolamine were observed to block the appearance of delta activity,[9] although the systemic effects of the large doses of these agents were marked.

Recent reports[10] noted that EEG and behavioral effects similar to atropine were achieved in patients with head trauma by intravenous diethazine—a phenothiazine compound with anticholinergic properties—with minimal systemic effects. In our continuing studies of the role of delta activity in electroshock,[3] the effect of diethazine was studied. It is the purpose of this report to describe the effects of diethazine on EEG patterns and on behavior of patients during electroconvulsive therapy, and to relate these observations to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

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From the Department of Experimental Psychiatry, Hillside Hospital.

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Read (in part) at the meeting of the Eastern Association of Electroencephalographers, New York, December, 1957. Awarded A. E. Bennett Psychiatric Research Award of the Society of Biologic Psychiatry, May, 1958.

Subjects and Methods

Forty psychiatric patients, at various stages of electroshock therapy in an open-ward, voluntary psychiatric hospital were studied. All observations were made in acute experiments in the EEG laboratory. After a routine EEG recording, diethazine was administered intravenously at the rate of 25 mg. per minute, for a total of 175 to 250 mg., depending upon the behavioral effect. The dosage varied from 2.8 to 4.0 mg. per kilogram of body weight.

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to those of atropine. In experimental animals, diethazine blocks the bradycardia, bronchospasm, salivation, fasciculation, and seizures induced by acetylcholine, fluorophosphate, and pilocarpine. It suppresses salivation and induces mydriasis and hypotension.[11]

EEG Analyses—Recording was continuous for the duration of the observation period, except during interview periods. Needle electrodes, and an eight-channel Medcraft instrument were used. All records were analyzed for the degree of delta activity,[3] the per cent time and principal alpha frequency, and the relative amount of fast activity. The alpha and delta activities were measured in anterior temporal-vertex, parietal-ear lobe, and frontal-occipital lead combinations.

Behavior Measures—Prior to drug administration an unstructured psychiatric historical interview and a structured questionnaire period[12] were tape-recorded. Following drug administration,

periods of recorded interview were alternated with EEG recording periods, until the EEG had again manifested the preinjection pattern on visual inspection.

Two estimates of behavioral effects were used: clinical descriptions by the participants—subject, interviewer, and technician—of the changes occurring during the drug period, and language analyses of the recorded interviews. Changes in language were evaluated by a syntactic analysis[12] and an analysis of the variability in verbal interaction in the dyad.[13,14,*] Both measures have been shown to be sensitive to alterations in behavior induced by changes in the central nervous system.

Observations

(a) Clinical.—Within two to five minutes of the start of the injection, subjects manifested spontaneous coughing followed by a dryness of the mouth and a thickness of speech. They reported a feeling of lassitude and a heaviness and weakness of the extremities, soon succeeded by increased restlessness and difficulty in maintaining eyelid closure.

Reports of visual and haptic illusory sensations, feelings of unreality and distance, and delusional thoughts about their illness, the setting of the test procedures, or our identity were voiced spontaneously by 18 subjects in the period between 15 and 60 minutes after drug administration. In three instances increasing agitation and panic led to a cessation of the recording. In two subjects withdrawal and negativism were the prominent behavioral response. Such patterns of behavior were transient and had disappeared in one and one-half to four hours in all subjects.

* Detailed analyses of these observations will be reported separately by Dr. J. Jaffe and Dr. R. L. Kahn.

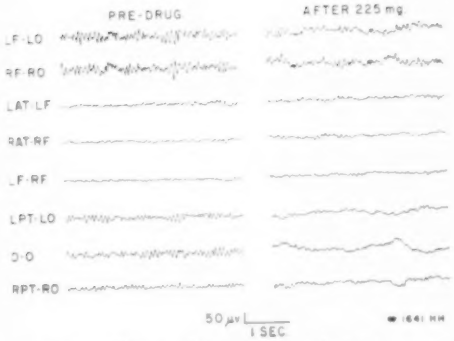

Fig. 1.—Effect of intravenous diethazine prior to electroshock in a man aged 27.

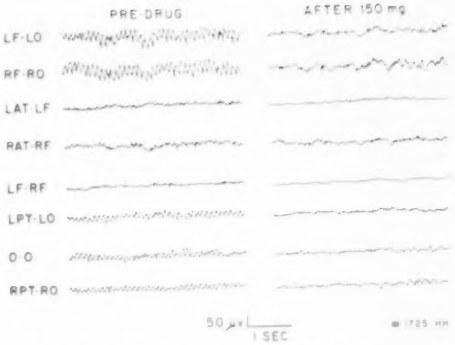

Fig. 2.—Effect of intravenous diethazine prior to electroshock in a woman aged 57.

(b) EEG Patterns.—Alteration in the EEG patterns was concurrent with the behavioral effects. In all records, changes occurred during drug administration and were sustained, with gradual diminution and restitution of the preinjection patterns, in one to five hours. The initial response was a decrease in voltage and desynchronization of all frequencies. There was a decrease in prominence of prevailing rhythms. In patients without delta activity (preelectroshock), desynchronization and voltage decrease were occasionally accompanied by low-voltage 5-7 cps activity, symmetric and prominent in frontal and anterior temporal leads (Figs. 1 and 2). The alpha frequency was not altered. The build-up in voltage and appearance of slower frequencies with hyperventilation were blocked.

In patients with varying degrees of high-voltage delta activity, desynchronization of the records became prominent, with a significant decrease both in voltage and in per cent time of slow wave activity. From an average per cent time delta of 45% in frontal-occipital leads, there was a reduction to a mean of 20%. Both random and burst delta activity diminished or disap-

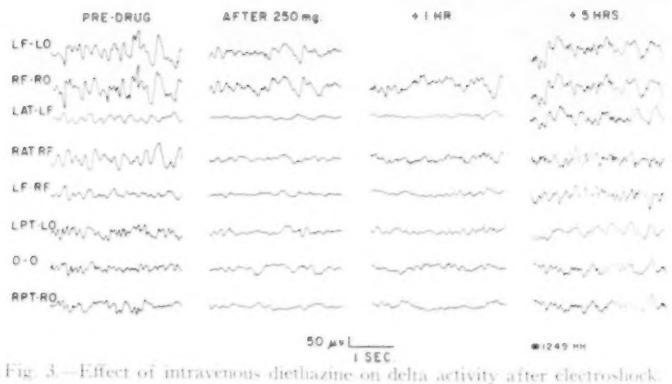

Fig. 3.—Effect of intravenous diethazine on delta activity after electroshock.

peared, and irregular low-voltage alpha and beta frequencies became prominent (Figs. 3 and 4). The hyperventilation response was no longer apparent.

(c) Language Patterns.—In previous studies, an intimate relationship between changes in syntactic language patterns and the behavioral response in electroshock had been reported.[12] With alteration in brain function, increased use of the third person, verbal denial, qualification, displacement, and clichés became prominent. These effects could be enhanced by the administration of intravenous amobarbital.[15]

In the subjects in the present study, syntactic analyses demonstrated a reversal of the patterns noted in electroshock. Use of the third person, qualification, and displacement decreased. Explicit verbal denial was modified and replaced by minimization and displacement, or by a reiteration of complaints of illness. In dyadic analyses, the verbal interaction was characterized by a greater diversity of vocabulary and less variability in the diversity scores for 25 word units.

The qualitative nature of these changes in the language patterns is opposite that of amobarbital and electroshock. The duration of language changes was concurrent with the changes in the electroencephalogram.

Comment

These observations confirm the report of Jenkner and Lechner[1] of the effects of diethazine in "normal" subjects.[10] Diethazine also alters electroshock-induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett and Johnson,[9] with minimal unpleasant symptoms. The effects of intravenous diethazine are immediate, both on the EEG and on

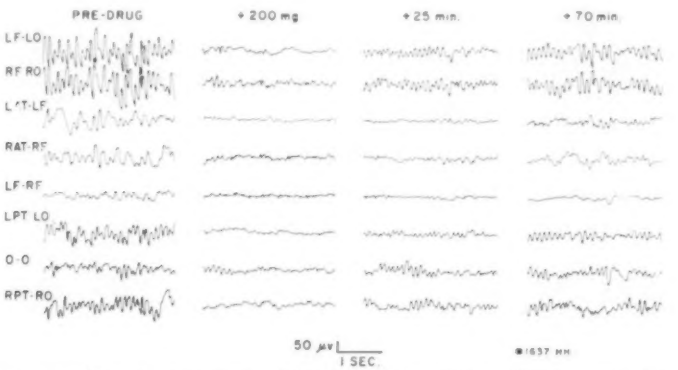

Fig. 4.—Effect of intravenous diethazine on delta activity after electroshock.

behavior, and thus provide a useful experimental agent with "anticholinergic" properties. Two aspects of these experimental observations warrant discussion: the role of acetylcholine-cholinesterase in the electroconvulsive therapy process, and the significance of diethazine "alerting" for concepts of hallucinogenic activity.

1. *Biochemical Basis of the Convulsive Therapy Process.*—While there has been considerable study of the psychologic and neurophysiologic aspects of convulsive therapy, little information concerning biochemical processes is available. The studies of biochemical changes following head trauma and spontaneous seizures provide some analogic data. Bornstein,[6] in a classical experimental study of head trauma in cats, demonstrated that within a few minutes after trauma free acetylcholine appeared in the spinal fluid and persisted for periods up to 48 hours. He further demonstrated a positive relation between the severity of head trauma and the quantity of free acetylcholine, the degree of electroencephalographic alteration, and the severity of the behavioral changes. The electroencephalographic records initially showed short periods of high-voltage fast activity, and a transient period of flattening of electrical activity, followed by prolonged periods of high-amplitude sharp waves in the delta frequencies. Concomitantly, alteration in consciousness, changes in reflexes, and posttraumatic seizures were most prominent with highest concentrations of free acetylcholine and greatest degree of EEG change.

Tower and McEachern[7] confirmed these observations in clinical studies in man. In 112 neurologic patients, free acetylcholine was found in the cerebrospinal fluid only in patients following head trauma and recent grand mal seizures, and the level of free acetylcholine varied directly with the degree of cerebral damage. In addition, these authors assayed the cholinesterase activity of the spinal fluid.[7,16] In patients following head trauma, they noted a sharp rise in nonspecific cholinesterase (benzoylcholine-splitting) and a drop in the specific cholinesterase (methacholine-splitting) activity of the spinal fluid. No such inversion was noted in fluids containing free acetylcholine following spontaneous seizures. Electroencephalograms were taken at varying intervals following trauma and demonstrated a direct correlation of the extent of EEG abnormality with the appearance of free acetylcholine in the spinal fluid.

Tower and McEachern also reported observations in six patients receiving electroconvulsive therapy. In patients after three to seven induced convulsions, they noted free acetylcholine in the spinal fluid in two patients and an increase in nonspecific cholinesterase with reversal of the cholinesterase ratio in five of the six. They concluded that the spinal fluid changes in electroshock are more like those of craniocerebral trauma than those found in epilepsy.† More recently, Sachs[17] confirmed the reports of free acetylcholine in the spinal fluid after head trauma and after electroshock.

In his studies, Bornstein[6] administered 0.5-1.0 mg/kg. of atropine and demonstrated a reversal or a blocking of the EEG effects and a modification of the behavioral and neurologic signs. Atropine also blocked the EEG and clinical signs induced by intracisternal acetylcholine.

Ward[8] applied these observations to the treatment of human subjects with varying degrees of head trauma. Subcutaneous doses of 0.1 mg/kg. of atropine induced both clinical improvement and reversal of EEG effects. These observations were recently confirmed by Sachs,[17] Ruge,[18] and Hughes.[19] On the basis of these observations, Ulett and Johnson[9] noted the effect of atropine and scopolamine in blocking the EEG changes of electroshock therapy. Concurrently, Jenkner and Lechner[10] reported

† Regarding the one patient of the six who failed to show either free acetylcholine or a reversal of the cholinesterase ratio, they noted: "It is interesting that this patient was the only one of the six to show no response to treatment."

effects similar to those of Ward, in studies of diethazine in cases of head injury.

Another group of investigations complete the available data. Studies of anticholinesterases, such as fluorophosphate, and tetraethylpyrophosphate (TEPP), which block the enzymatic breakdown of acetylcholine, demonstrate the development of high amplitude rapid-frequency EEG patterns similar to those of status epilepticus, as well as slighter degrees of abnormality, as noted in post-traumatic states.[20-23] In these studies, atropine blocked both the electroencephalographic and the clinical toxic effects.

Thus, from both experimental and clinical studies of craniocerebral trauma we may assume that (*a*) the acetylcholine activity of the spinal fluid increases, (*b*) pseudocholinesterase activity increases, with a reversal of the ratio of cholinesterases, (*c*) EEG hypersynchrony and slowing parallel these biochemical alterations, and (*d*) anticholinergic agents may block both the electroencephalographic and the clinical effects. From the data available, it is probable that the biochemical basis of convulsive therapy is similar to that of craniocerebral trauma. Convulsive therapy results in free acetylcholine in the spinal fluid[7,17] and a reversal of cholinesterase ratios.[7,16] The electroencephalographic effects of repeated induced convulsions is the development of high-voltage, symmetric, slow-wave activity, occasionally with spike activity,[3,24,25] which is similar to that observed in severe head trauma.[26,27] In previous studies we have reported the relationship between the degree of induced slow-wave activity and behavioral response.[3] The studies reported here and the work of Ulett and Johnson[9] demonstrate a reversal of the EEG and the behavioral effects of convulsive therapy by anticholinergic compounds. In each characteristic, convulsive therapy is thus similar to cerebral trauma. While the acetylcholine-cholinesterase system is highlighted by these studies, other enzyme systems may also be altered.[17] These studies also suggest that convulsive therapy provides an excellent experimental method for studies of craniocerebral trauma.

Studies of the brain-stem-activating system by Jasper and Droogleever-Fortuyn[28] and Lindsley et al.[29] had laid the foundation for the prevailing conclusion that symmetric EEG slow-wave activity has its origin in mesencephalic structures, and that these structures intimately affect the states of "alerting" and "drowsiness." More recently, Rinaldi and Himwich[30,31] have related the site of action of atropine and cholinergic drugs to this mesodiencephalic activating system. It is also probable that these structures may be selectively affected by the convulsive therapy process, and that both the clinical and the electrographic effects may be intimately related to changes in this system.

2. Diethazine "Alerting" and Hallucinogenic Activity.—The behavioral effects of diethazine provide information regarding another aspect of the convulsive therapy process. In patients without prior convulsive therapy, illusory phenomena and feelings of unreality were observed. These were similar to the hallucinogenic effects of lysergic acid diethylamide (LSD[32]) and mescaline.[33] Again, analogic data about the clinical and EEG effects of these agents may provide some information about convulsive therapy.

In studies of mescaline, Wikler[34] noted that the EEG demonstrated no change, or intermittent or continuous low-voltage fast activity, or increase in alpha frequency. Denber and Merlis[35] noted a similar acceleration of alpha frequency, decrease in per cent time alpha, including its disappearance, and nonspecific random beta activity. Delta activity did not occur. In patients with delta activity induced by electroshock, Merlis and Hunter[38] noted that intravenous mescaline markedly diminished the amplitude and per cent time delta activity with an increase in per cent time alpha activity.

The effects of LSD on EEG are similar. Gastaut et al.[36] noted an acceleration of alpha frequency of 0.5 to 4.0 cps, with an

accentuation of beta rhythms. Rinkel et al.[37] confirmed this observation and noted, in addition, a reduced responsivity to hyperventilation.‡

In summarizing his studies, Wikler[34] concluded that "regardless of the . . . drug administered, shifts on the pattern of electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness." This generalization provides a meaningful construct in which these agents may be assessed. Agents that evoke EEG desynchronization tend to be hallucinogenic, and mescaline and LSD are clear examples. Agents that synchronize frequencies, such as barbiturate and meprobamate in the beta frequency range, and chlorpromazine, promazine, and perphenazine in the delta frequency range[39] tend to be sedatives, euphoriants, and relaxants.

The observations on diethazine reported here are consistent with this hypothesis. In patients without delta activity, the EEG demonstrated desynchronization of frequencies, and this was associated with clinical illusory phenomena. In patients with delta activity desynchronization occurred, and alerting and reversal of the speech patterns induced by electroshock were observed.

Electroconvulsive therapy may also be understood in this framework. We have previously noted a direct relationship between clinical evaluations of improvement and the degree of EEG slowing induced by electroshock.[3] Under these conditions, sedation and euphoria are most prominent, and hallucinatory activity diminished. In patients in whom hypersynchrony is not induced, behavioral change is limited, and "improvement" does not occur.[4]

Previously we have concluded that the mode of action of convulsive therapies is based on the induction of a state of altered cerebral function, in which changes in adaptive interpersonal behavior occur, and are interpreted as "improvement."[3,4,39] The present studies amplify two aspects of this neurophysiologic-adaptive hypothesis. The biochemical substrate of the behavioral change is reflected by an alteration in the acetylcholine-cholinesterase relationships of the central nervous system. It is also probable that EEG hypersynchrony provides the neurophysiologic basis of the milieu change, which is clinically manifest as sedation and euphoria and is evaluated as "improvement."

The neurophysiologic-adaptive hypothesis of convulsive therapy has provided a meaningful basis for studies of other physiodynamic therapies.[39] In this study, it has been possible to amplify our understanding of neurophysiologic aspects of hallucinogens as well.

Summary and Conclusions

The effect of an anticholinergic agent, diethazine, on the EEG, behavior, and language patterns was observed in 40 psychiatric patients, at various stages in the course of electroconvulsive treatment.

(*a*) Behavior: Increased restlessness and agitation, haptic and visual illusory sensations, and delusional thoughts about their illness or the examiner's identity were observed.

(*b*) EEG: Alteration in EEG were concurrent with behavioral changes. There were a decrease in voltage and desynchronization of all frequencies. In patients with delta activity, the per cent time and voltage of delta activity decreased.

(*c*) Language: Syntactic patterns described for convulsive therapy were reversed. Use of third person, qualification, and displacement decreased. In dyadic analyses there was a decrease in the coefficient of variation.

‡ Studies are now in progress on the effects of LSD, Win-2299 (2-diethylaminoethyl-cyclopentylhydroxy-2-thienylacetate), benactyzine, and other anticholinergic compounds on postconvulsive EEG delta activity. Initial experiments with these compounds have demonstrated marked diminution in per cent time and amplitude of delta activity associated with behavioral changes similar to those seen with diethazine.

These observations are discussed in the framework of the neurophysiologic-adaptive hypothesis of the action of convulsive therapy, and it is concluded that (*a*) the biochemical basis for convulsive therapy is similar to that of craniocerebral trauma; (*b*) changes in acetylcholine-cholinesterase metabolism are intimately related to the behavioral effects, and (*c*) EEG desynchronization may be a physiologic concomitant of hallucinogenic activity, and EEG hypersynchrony, associated with euphoria and sedation.

Mrs. Hannah Mosquera gave technical assistance in the EEG recordings, and Dr. Joseph Jaffe and Dr. Robert L. Kahn made the analyses of the tape recordings.

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Azacyclonol (Frenquel) in Chronic Schizophrenia

Objective Measurement of Its Effects

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Introduction

Since studies on azacyclonol first appeared in the literature, in 1955, many investigators have praised azacyclonol as an anticonfusional, antidelusional, and antihallucinatory drug. Cohen and Parbour [6] have claimed that azacyclonol is as effective an ataraxic agent as chlorpromazine or reserpine. Most descriptions of the effects of azacyclonol have been ambiguous and subjective. Results are frequently reported in such vague terms as "complete remission," "greatly improved," or, simply, "improved." However, three studies using a double-blind cross-over design [27,29] have also indicated beneficial effects of azacyclonol. A minority of studies have shown azacyclonol to be ineffective,[3,16,24,30,32,35] including a well-designed study done with a double-blind technique by Peak, Canestrari, and Roebuck,[24] which showed no significant difference between azacyclonol and placebo groups of chronic schizophrenic patients. Cutler, Monroe, and Anderson,[7,8] in studying the effects of "tranquilizers" upon pathological behavior in schizophrenics, have stressed the importance of doing adequately controlled studies with precise measurements of drug-induced changes and well-defined criteria of disturbed behavior.

The purpose of the present study was to evaluate the effects of administration of azacyclonol on behavior and thinking processes in chronic schizophrenic patients, utilizing multiple observational techniques, including standardized rating scales. To overcome some of the ambiguity and subjectivity mentioned above, each patient's pathological behavior was defined and quantified in the present study as was done in the studies of Cutler and his co-workers. In addition, the Fergus Falls and Lorr rating scales [18,19] were used to measure other dimensions of patient behavior. Finally, appropriate statistical techniques were applied to test the significance of drug-induced changes.

Material and Method

Subjects and Observers—The experimental group consisted of 20 schizophrenic men, hospitalized from 8 to 45 years. Ages ranged from 31 to 75 years. Eleven of these patients had previously received chlorpromazine and reserpine, the last dose having been given several months before the present study began. Eight patients had had insulin coma therapy, the latest in 1954. Seven of these eight patients had also had electric shock therapy, the latest series in 1953. One of these seven had a frontal lobotomy in 1950. Two patients had electric shock therapy only. Seven patients in this study had had no previous somatic or ataraxic treatment.

During the entire period of the study patients were given no drugs other than the experimental medication and no additional treatment other than routine ward care. The diagnosis was chronic schizophrenia in all cases, with 10 originally diagnosed as a mixed type, 7 as paranoid, 1 as hebephrenic, and 1 as catatonic.

Drugs and Dosage—The dosage of azacyclonol was 40 mg. given orally three times daily. This amount was considerably higher than the dose recommended at the time by the Wm. S. Merrell Company and by those investigators reporting favorable results. Placebo and drug were identical

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in appearance. No problems occurred in the acceptance of medication, and the patients were carefully observed to see that they swallowed their medication.

Experimental Design.—A double-blind cross-over design was used. The pharmacist, who worked in a separate building and had no contact with the patients, divided the 20 patients into two groups of 10 each, selecting them at random. It was not known by patients, observers, or experimenters which patients received azacyclonol and which received placebos until the conclusion of the study.

An initial four-week control period, during which neither placebos nor azacyclonol was given, was followed by a six-week medication period in which one group of 10 patients received azacyclonol and the other group of 10 received placebos. In the subsequent six-week period, the groups were reversed, with the original placebo group receiving azacyclonol and the original azacyclonol group receiving placebos. A four-week drug-free observation period followed. One advantage of this experimental scheme is that each patient serves as his own control.

Three male psychiatric aides with long experience in handling psychiatric patients formed one group of observers. The aides were trained in the necessary observational techniques prior to beginning the study. The aides were told only that we were studying the effects of a new drug on mental illness. They were not told the name of the drug, previous results with it, or any expected effect. Two psychiatrists, who served as the other observers and supervised the study, had known the patients for periods up to 15 months. Meetings were held four times per week with the aides, and sympathetic attention was given to any of the problems involved in the study. The aides spontaneously expressed their appreciation of these meetings and felt that they were a part of the research team.

A specific picture of each patient was gained over a period of several months before beginning the study by having aides and physicians list habitual pathological behavior traits of each patient. Then the nursing notes were reviewed for other typical patterns of pathological behavior to include on the list. The patients were then observed by the two psychiatric investigators, and a list of significant pathological behavior traits characteristic of each patient was selected. The aides were then trained in the observation of these traits, and ambiguous phrases were changed so that all agreed on the meaning of terms.

Once the final list was made up for each patient, it remained the same throughout the study. Each symptom was listed by number, for ease in recording. Ward data sheets had seven columns, one for each day of the week; and eight hours, one for each hour from 8 a. m. to 4 p. m. (Cutler et al.,[5] using this same technique, found that observations from 4 p. m. to 8 a. m. did not materially affect activity scores computed on an 8 a. m. to 4 p. m. basis.) The aides made hourly notations by number of the presence or absence of traits over the eight-hour period. Space was provided for additional comments on unusual behavior and events of special significance occurring on the ward during the particular week for which the rating sheet was completed. Pathological activity scores were computed by adding up the number of hours per week in which one or more of the traits on the list were observed.

An example of a typical trait rating list follows. With Patient 1, the traits noted were as follows: (1) talks to self or hallucinates; (2) paces; (3) plays imaginary musical instrument; (4) chain smokes.

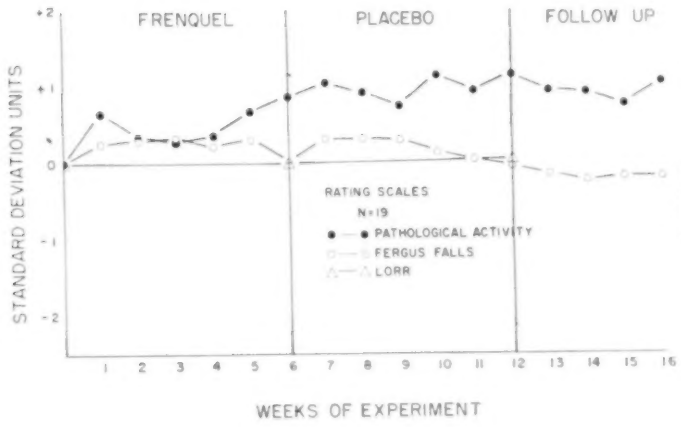
Somnolence was noted whenever it occurred during the 8 a. m. to 4 p. m. period. This was considered important because any lessening of activity might be related to daytime sleeping, and thus one "symptom" be substituted for another.

The aides also filled out a Fergus Falls behavior rating on each patient weekly. The Fergus Falls Scale measures a number of significant areas in a patient's ward adjustment, including response to meals, response to other patients and doctors, psychomotor activity, speech, toilet behavior, etc.

The psychiatric investigators evaluted the patients during each phase of the study by mental status examinations and by administration of the Lorr Scale, a 40-item comprehensive rating of many aspects of the patient's thinking and behavior. The psychiatric interview included examination of thinking and reasoning, judgment, orientation, affect, behavior, and the presence or absence of delusions or hallucinations. Careful nursing notes by personnel on all shifts on the ward were also kept on each patient, and these were correlated with other measures by the investigators.

During the initial observation period, observer interreliability was determined by having the three aides make simultaneous independent observations on the trait scales and Fergus Falls Scale. Rank-order correlations were computed to test the reliability of the total score, as well as specific symptoms. The same three aides were used throughout the study. The psychiatric investigators rated the whole group independently of each other during the same initial period, and their interreliability was estaldished.

During the 20-week period of the study each patient had hourly observations during the day, weekly Fergus Falls Scale ratings, three mental status examinations, and three Lorr Scale evaluations.



Mean changes in pathological behavior produced by azacyclonol in chronic schizophrenic patients.

Laboratory studies were done every two weeks. These included white and red blood cell counts, differential count, and urine examination, including urine bilirubin determination. In addition, examination of the skin and motor neurological system was done regularly.

To test the possible statistical significance of any changes induced by the drug, the weekly behavior ratings and Fergus Falls Scale rating were compared with the control period, making use of the *t*-test for repeated measurements on the same subjects.[5] The three ratings obtained from the Lorr Scale were tested in the same fashion. To test the significance of any cumulative changes, analysis-of-variance techniques making use of double classification with *m* scores per cell were used.

To allow direct comparison on a graph, the three sets of scores were reduced to standard-deviation units and are presented in this fashion in the Figure.

Results

Pathological Activity Scores.—Table 1 shows that the least active patient during the control period had a mean activity score of 24, which was more than three times the standard deviation of the group mean (6.68). Pathological activity scores were therefore sufficiently elevated and stable at the beginning of the experiment to permit the statistical evaluation of changes in scores that might occur during the study. Interrater reliability was established by computing rank-order correlations of the observers' ratings. These correlation coefficients ranged from 0.91 to 0.93, indicating a degree of reliability among the raters which meets the standards usually required.

The number of behavioral signs which characterized individual patients ranged from 2 to 7, with a mean of 3.8. The specific behavioral symptoms and the number of patients displaying them are shown in Table 2. The total number of symptoms listed for all subjects was 40.

TABLE 1.—*Means and Standard Errors of Pathological Behavior Measures*

	Activity	Fergus Falls	Lorr
Group A			
1	49	19.5	13.98
2	46	21.0	10.64
3	50	19.5	12.30
4	44	24.0	11.98
5	35	19.0	15.92
6	49	22.0	13.61
7	42	18.0	14.32
8	49	17.0	12.08
9	38	21.0	17.29
Group B			
10	43	26.0	10.64
11	24	33.0	16.57
12	32	19.0	11.76
13	47	10.0	10.21
14	47	21.5	9.50
15	44	21.5	12.13
16	50	26.0	8.71
17	46	30.0	10.50
18	47	28.0	10.92
19	41	28.0	9.33
M *	43.32	22.84	11.86
S. D.	6.68	3.31	2.22
S. E.	1.53	0.99	0.51

* Mean scores for control period.

TABLE 2—*Pathological Behavior Signs*

Symptom	Patients Displaying Sign
1. Talks to self or hallucinates	17
2. Curses	14
3. Paces	15
4. Gestures	2
5. Grimaces	3
6. Scratches himself	1
7. Talks to others in scrambled speech	1
8. Whistles and sings	1
9. Hurries about	2
10. Throws things out window	1
11. Eats fast	1
12. Throws tray	1
13. Inappropriate laughter	1
14. Grinds his teeth	1
15. Shoves broom vigorously	1
16. Kicks and hits at imaginary figures on wall	1
17. Gets angry at people	1
18. Draws small figures	1
19. Sings	1
20. Seclusive	2
21. Inappropriate talk	1
22. Sings and curses	1
23. Rubs his eyes	1
24. Scrambled speech	2
25. Uses phrase "same old story"	1
26. Hostile when questioned	1
27. Lies on floor or table	1
28. Nervous	1
29. Furtive	1
30. Jabbers or laughs at imaginary figures	1
31. Walks floor in same spot	1
32. Jumps up and down	1
33. Stares at ceiling	1
34. Picks at skin	1
35. Shakes matches like dice	1
36. Picks up pieces of paper, dust, tobacco	1
37. Outbursts of angry talk	1
38. Sleeps during day	6
39. Plays imaginary musical instrument or conducts imaginary orchestra	1
40. Shakes fist	1
41. Draws or prints	1

Since it was noted in previous studies that a decrease in pathological activity when tranquilizing drugs are administered is often accompanied by an increase in sleep, a notation was made on each patient's behavior rating chart for any hour during which he was observed sleeping. Only six subjects were recorded as sleeping during normal waking hours, and no increase in sleep occurred during the time they received the drugs.

Group A, given azacyclonol during the first six weeks of the study, showed no significant change in activity scores. One subject became ill from a previously existing condition during the study, and his scores were not included in computing the group means, although including them would not have altered the curve.

Group B were given azacyclonol during the next six-week period of the study. They, also, displayed no significant change in activity. Since the activity curves for the two groups were very similar, they were combined to form the curve seen in the Figure.

The over-all levels of activity observed during the drug and the placebo period were tested for significance by use of analysis-of-variance techniques. These results also indicated no significant difference between the two periods.

Fergus Falls Behavior Rating Scale—The rank-order correlation coefficients establishing interrater reliability in the Fergus Falls Behavior Rating Scale range from 0.57 to 0.84, with a median of 0.74. The weekly ratings for the patients in both groups were tested against the control period, but the differences at no time reached a level of statistical significance. Analysis of variance of the scores of the drug and placebo periods also failed to indicate any significant difference. The curve plotted in the Figure is based on the mean score of the combined groups.

Lorr Multidimensional Scale for Rating Psychiatric Patients.—To obtain an over-all estimate of each patient's adjustment as measured by the Lorr Scale, the absolute sum of the deviation of each rating from the norm given by Lorr was used. No difference approaching statistical significance was obtained in the three ratings. As with the other rating techniques, interrater reliability was established by rank-order correlation, the coefficient in this case being 0.94.

The impression of the two psychiatrists who performed the mental status examination was that no clinical change had taken place in the patients as a result of treatment. Examination of the nurses' notes during the experiment also showed little change when they were compared with notes that had

been written before the beginning of the study.

No selective effect on delusions, hallucinations, or confusion was found.

No toxic side-effects were observed.

The results found support the previous negative findings of the effectiveness of this drug by Sarwer-Foner [32]; Peak, Canestrari, and Roebuck [24]; Turner and Merlis [35]; Rosner, Fierman, and Kramer [30]; Lemere,[16] and Barsa and Kline.[3] However, our findings are at variance with the beneficial effects of azacyclonol previously reported by numerous authors.[1,5,6,9-11,17,20,22,25-29,34]

Comment

The procedures used to quantify pathological behavior in this study offer many advantages over the usual techniques reported in the literature by greatly reducing subjectivity in the observations and providing a numerical score which can be statistically tested. These methods can be applied to the study of drug effects under a variety of conditions and with different types of subjects.

Previously reported studies, using in part a similar methodology,[7,8] showed that chlorpromazine decreased pathological behavior and increased sleep, and that reserpine produced no decrease in pathological behavior and increased sleep in chronic schizophrenic patients, as contrasted with this study, which showed that azacyclonol produced no decrease in pathological behavior and no increase in sleep in chronic schizophrenic patients.

Those who have previously reported beneficial results with azacyclonol have stated that higher doses are not superior to moderate doses in producing these results, and amounts of up to 1200 mg. daily have been given with no stated increase in improvement.[6,11,29]

It was our feeling that the Lorr Scale did not contribute meaningful information to the present study, was unwieldy and time-consuming, required subjective judgments on the part of the rater, and was productive of no more significant information than an adequate mental status examination.

Summary and Conclusions

Nineteen chronic schizophrenic men, divided randomly into two groups, were intensively studied by a double-blind crossover design for a total of five months to evaluate the effectiveness of azacyclonol (Frenquel). A daily dose of 120 mg. of azacyclonol had no significant effect on the thinking or behavior of these chronic schizophrenic patients. Extravagant claims for this drug made by some previous investigators were not supported by this study.

Azacyclonol (Frenquel) was supplied by the Wm. S. Merrell Company, Cincinnati.

115 E. 82d St. (28)

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Technique for Measuring Heart Potentials Continuously in a Freely Moving Rat

EDWARD M. EISENSTEIN, A.B., and MORRIS H. WOSKOW, A.B., Los Angeles

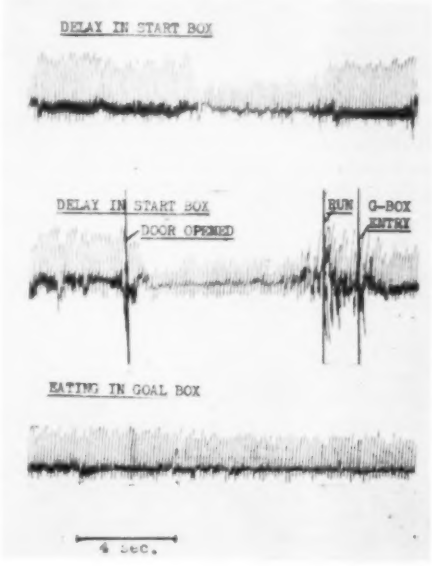
It is often desirable to record a physiologic variable continuously without restricting movement. For example, one might wish to know the sequence of heart rate changes demonstrated by an experimental animal during the learning of a maze. Techniques of recording heart potentials in the rat have been reported [1,2] but do not allow the animal to move freely during recording. The following technique represents a simple procedure for such continuous recording in a freely moving rat.*

Two metal surgical sutures (Tru clip #904) are used as electrodes. They are clamped bilaterally on the back of the anesthetized animal about 1 in. from the dorsal midline and just above the scapula, so that they are some distance from moving limbs and in loose skin. The clips cause no apparent irritation and will remain intact for two weeks or longer. Although initial work involved shaving the skin before application of the sutures, this has proved both unnecessary and undesirable, in that shaving appears to attract the animal's attention to the electrodes.

When heart potentials are recorded, two Mueller #30c alligator clips soldered to two lengths of Belden #8014 indoor aerial wire are clipped to the sutures on the rat's back. The leads are then connected to an appropriate amplifier and recorder. If the intertwined leads are suspended over a hook or pulley above the apparatus and allowed to hang freely without too much slack, the rat does not often get entangled. Both the clips and the sutures are available in different sizes and can be selected according to the size of the animal.

We are employing this technique in a study of heart rate changes of the rat in a learning situation involving a start box, a 7-ft. runway, and a food box. Although the results of this study will be reported later, it may be of interest to report at this

Continuous recording of heart rate of the rat in a freely moving situation.



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Department of Psychology, University of California at Los Angeles.

* Prof. J. A. Gengerelli first suggested the technique reported herein. Through the use of Prof. M. A. Wenger's laboratory, this work was aided, in part, by Research Grant M-788 from the Institute of Mental Health, National Institutes of Health, U. S. Public Health Service.

time on the readability of the records obtained thus far. The amount of "noise" during movement remains relatively constant and of low amplitude (Figure). When the animal is quietly eating in the food or goal box, approximately 98% of the records are readable.† Typically, there is more movement in the start box, and still more, of course, in the runway. Here readability drops to approximately 87% and 68% respectively. The Figure shows samples of a record obtained from a rat delayed in the start box for 60 seconds and then allowed to run to the food box.

The record was obtained on an Offner Type D3 Electroencephalograph with a chart-paper speed of 0.625 cm/second. It will be seen that the heart rate is readable in each situation. For this rat, the rate proved to be 480 beats a minute in the food box and 450 beats a minute in the start box. Such values appear to be typical among our data, and approximate more closely the results reported by Dessaux[3] than those reported by Farris and Griffith.[4]

Department of Psychology, University of California at Los Angeles (24).

† Readability of a record is defined as the ratio of the number of centimeters of obtained record in which heart beats can be clearly counted to the total number of centimeters of record × 100. A median ratio was then calculated for readability in the start box, runway, and food box, utilizing the combined data of three rats during a total of 30 trials. The ratios thus obtained were used as indices of percentage readability.

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Books

BOOK REVIEWS

Your Speech Reveals Your Personality. By Dominick A. Barbara. Price $4.50. Pp. 174. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958

The author's belief is that speech and personality are one, and he sets out to emphasize the fact that speech not only has the function of communicating information to others but also is capable of revealing the speaker's relationship to himself and others. There is no presentation of experimental studies by the author to substantiate these already rather well-popularized concepts. Instead, the corroborative statements of other writers are cited or everyday examples are given of the association of speech peculiarities and specific personality characteristics. For example, the "self-effacing speaker" is said to have a fear of triumph and also a fear of failure, and his anxiety at being looked at and discovered is associated with typical speech mannerisms. The "expansive speaker" and the stutterer are other examples discussed of the association of customary personality conflicts and typical speech mannerisms.

The author is obviously quite interested in the problem of stuttering; in fact, in his prefatory remarks to this small volume, he acknowledges that this book is an outgrowth of his previous book on stuttering. From this reviewer's perspective the strongest part of the book is, in fact, the section on stuttering. The concepts expressed in the rest of the book regarding the relationship of speech and personality have, for the most part, been adequately and well disseminated among psychiatrists, and what is now in order are more rigorous experimental and clinical studies to shape up these concepts. In reading this book, most psychiatrists are likely to be disappointed and feel they have learned nothing new but have been reminded of some familiar generalizations.

The book would have more to offer the speech therapist and speech teacher, the graduate student in psychology and social work, for they would be more likely to benefit from the author's earnest effort to integrate and synthesize several different approaches to verbal communication as it is affected by personality variables.

LOUIS A. GOTTSCHALK, M.D.

On Not Being Able to Paint. By Marion Milner. Second Edition, with a foreword by Anna Freud. Price, $4.50. Pp. xxii + 184, with illustrations. International Universities Press, Inc., 227 W. 13th St., New York 11.

Our knowledge and understanding of the creative process has several sources—the memories and introspections of creative persons; the analysis of creative products, with or without firsthand knowledge of the history and personality of the creator, and accounts of the psychotherapeutic or psychoanalytic experiences with (or by) persons who came for psychiatric help generally as a means of overcoming the blocks to their creativity. Furthermore, our knowledge of the creative process is generally limited to those persons who have achieved some degree of eminence. Marion Milner's book differs from previous works in this field in that it concerns itself not with eminently creative persons but with the "Sunday painter" and the problems that may inhibit his creativity. Her work also differs from others in that she combines both her knowledge of and experience in psychoanalysis (personal as well as with her own patients) with her experiences in learning how to paint.

The author is both experimenter and subject in the book. Throughout most of the book, which, with the exception of the Appendix, is written primarily for the layman, the author's experiences with free drawings are utilized as illustrations of psychoanalytic principles or theory. No attempt is made to test the validity of these ideas or to compare them with other theoretical formulations. It is, therefore, not surprising that Anna Freud, in her foreword to the book, should point out the similarity between the difficulties that the author encountered in her artistic venture and those that patients encounter in the process of free association. Fear of relaxing rational control, fear of the lack of differentiation between subject and object, and a lack of confidence in the integrative forces of the ego are some of the factors

that are common to both processes. Indeed, the absence of these fears has also been pointed out by others who have investigated the creative process in the eminently creative.

While the layman will find most interest in the author's discussions of her experiences in overcoming the obstacles to her own creativity, the psychiatrist and the serious student of the creative process will be most concerned with the Appendix, in which the author deals more with theoretical formulations. Here the author's thesis is "that psychic creativeness is the capacity for making a symbol" and that prelogical and nonverbal ways of thinking about this capacity affect the way in which this capacity works for us. The inhibition of this capacity, it is suggested, is to be found in the extremely idealized notions that some people have of what their products ought to be. When they become disillusioned with their products, they give up their attempts to produce anything. This inhibition is traced to "the original discovery that their faeces are not as lively, as beautiful, as boundless, as the lovely feeling they had in giving them."

In his symbols, the artist conceptualizes his own vivid experiences, which are a combination of internal and external perceptions. While other analysts may regard the function of the symbol or of artistic creativity as a means of recovering the lost object (a manifestation of the depressive position), Milner suggests that the art product is concerned with an earlier stage, a stage in which this individual was aware of others and which makes subsequent sadness at loss possible. Thinking about art as a recreative experience may have a technical function for the analyst who has the artist as patient. But the artist as artist is not recreating experiences but creating what is as he perceives it. This differentiation between artist as artist and artist as patient is indeed a valuable one. It raises the question whether in studying the creative process with a theory that is based on experiences with patients we are not likely to overlook some of the constructive aspects of the creative process that make it a truly constructive experience. And, by the same token, it raises the question whether a complete theory of personality can be based on studies of patients to the exclusion of well-functioning adults.

While the author's views on the artist as patient are not too dissimilar from those of other psychoanalysts, it is to be hoped that the author will continue her investigation of the dynamics in the artist as artist, for here is a relatively unexplored area that will contribute much to our understanding of the creative process.

MORRIS I. STEIN, PH.D.

Bases physiologiques et aspects cliniques de l'épilepsie. Published under the direction of Th. Alajouanine. Price, 2300 fr. Pp. 274. Masson & Cie, 120 boulevard Saint-Germain, Paris 6e 1958.

This material, concerned with the second of a series of neurophysiological weeks held at the Salpêtrière, was collected by Antoine Rémond. The first collection, concerning the Major Activities of the Temporal Lobe, was published in 1955. The present collection does not pretend to make a summary of all our knowledge of the vast subject of epilepsy. It envisages only some essential problems of physiological nature. Bremer studies excitation and inhibition in the epileptic process; Fessard, the mechanisms of interneuronal synchronization in the epileptic attack; Morin, the circulatory-vegetative correlations in experimental epilepsy; Walter presents some novel conclusions based on the study of signals of low voltage; Gastaut studies neuronic discharges distant from the epileptogene lesion; Castaigne, Buge, and Lecasble make an electroclinical correlation based on 100 cases; Penfield studies temporal attacks; Alajouanine and Gastaut describe synkinetic-startle and epileptic-startle; Gastaut studies psychomotor epilepsy; Lecasble, myoclonic epilepsy; Heuyer, the evolution of infantile epilepsy, and Ledeboer, the medicosocial aspects of epilepsy.

This list will give an idea of the rich harvest of information which this collection contains. Since much of the material consists of summaries of matter still under study, there is little to be gained by trying to summarize the summaries. Those who work in this field will know which studies bear on their own interests. They will find here the thinking and experience of acknowledged masters in the field of epilepsy.

We may look forward to the publication of other collections in this series, of which one, concerned with the activities of the occipital lobe, is in press and another, concerned with the rhinencephalon, is being prepared.

PERCIVAL BAILEY, M.D.

Facts and Theories of Psychoanalysis. Third Edition. By Ives Hendrick, M.D. Price, $6.00. Pp. 385. Alfred A. Knopf, Inc., 501 Madison Ave., New York 22.

The first edition of this book appeared in 1934; the second, in 1939. Now, almost twenty years later, the third edition is presented with considerable modification and expansion. The author is one of the early American psychoanalysts who obtained his training from the first newly immigrated foreign psychoanalysts. Dr. Hendrick had a sound and basic training and has contributed many original investigations to the general field of psychoanalysis, concerned both with theory and with practice. He has risen high in the American psychoanalytic group, having been president of the national association. All who know him respect him for his dedication and learning, and also for his originality and interest in research and modification of psychoanalytic theory and practice.

In the first part of the book the author presents what he calls the facts of psychoanalysis, which are the statements of those assumptions considered to be conclusively proved in this field. The second part deals with the theoretical concepts of psychoanalysis, which are largely derived from Freud's original studies, although somewhat modified and supplemented by the work of his followers. The third part deals with therapy by psychoanalysis, in which many pragmatic points are discussed. Considerations of the psychoanalytic movement are taken up in the fourth part, in which the relationship of psychoanalysis to dynamic psychiatry, child analysis to child psychiatry, psychoanalysis to diseases of the body, and applied psychoanalysis are discussed. There is a portion added to this section which deals with psychoanalysis as a profession and considers psychoanalytic education, the early controversies in the field, and some of what he calls "second-generation controversies." This portion is to a great extent historical and extremely interesting, as written by a person who has been in the thick of the development of psychoanalysis in this country from the very beginning.

The book is extremely well written and easy to understand. It is directed to the intelligent layman, but the general physician certainly can profit from it. As a matter of fact, this is an extremely worth-while book to give to psychiatric residents, or even beginning candidates in psychoanalytic training, because it covers most of the empirical and theoretical data of the field. The author does not make dogmatic statements but presents his facts as he sees them and the arguments that have developed around him. Thus, his descriptions of the various aspects of psychoanalysis are extremely palatable and do not lead to incorrigible bias on the part of the reader.

There is a large and informative glossary at the end of the book and an extremely good index. In addition, a small but excellently chosen list of books is suggested for further reading.

ROY R. GRINKER, M.D.

The Psychological Study of Man. By John Money, Ph.D. Price, $4.75. Pp. 226, with 1 illustration. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

Charles C Thomas, in another one of this publisher's commendable and provocative volumes, has presented Money's work in a convenient and readable format. The book itself attempts a synthesis of some of the relatively disparate concepts in psychiatry and thinking about communication today. Money tries to draw together language and behavioral postulates and to place them in the cultural ground substance within which they are properly enclosed. He provides an exceedingly brief historical note and goes on to propose a biodynamic unity in place of the Cartesian mind-body duality. Mind, he defines as "the information and communication function of the human organism," but, as he says, these are intrinsically bound up with physiology, and thus he proposes a "body-mind" integrum. This is perhaps more semantic preciosity than a real conceptual advance, however.

In the context of the human being as a signaling and receiving apparatus, Money fractionates the information agencies of the ego into three categories: (1) "decipherment appraisal," which he calls *spectatorship*; (2) "mastery over yielding and collapse," which he calls *mastery*, and, finally, (3) "control of mastery and attack," which he calls *control*. Although couched in somewhat different language, such a division is subject to the same criticism of artificiality, and in effect Money proposes that objection for the mind-body difficulty. It is also a discrimination quite possibly misinterpreted by the literalist as may be the id, ego, and superego, which it suggestively resembles. These three ego functions Money relates in a sort of vague matrical manner, which would appear to derive from Adolph Meyer's notion about the multifactorial causation of mental operations and aberrations.

A set of five "inevitables" which are operative in a sort of overriding fashion in the ego's activity is postulated, namely, (1) aggregation (the "social symbiosis" of man), (2) ecological setting, (3) subspecies status ("carcass-things that function," and may be denominated and grouped), (4) sexual status, and (5) death. Several of these are self-explanatory. Money, by this approach and the discussion of "inevitables," adroitly, and, again, perhaps semantically only, avoids the use of the concept of needs and drives, which these items have been called by others.

Pursuing this formulation, he proceeds to derive a way of describing and including many, if not most, of our ways of viewing the various clinical entities with which we are confronted. There are hints of rather interesting insights scattered throughout the pages of the book. For example, he views the hallucinating schizophrenic as an aberration of "chronic spectatorship" and remarks that "knowing comes to a temporary rest with the formulation of either a delusion, belief or fact (protofact)." Unfortunately, many of these are hinted rather than more fully developed. "Free association," he says, is "oblique inquiry," and thereby signals the individual to communicate primarily about himself.

The author presents interesting attempts to partition further, in terms of degree, frequency, and context, his larger categories, such as control. Psychological states are sketched, although any attempt to assign causality is studiously avoided, and case material is briefly included. He speaks of drug states briefly and says that the "greatest therapeutic successes to date have been achieved through disorders of excessive use of the control function." Such important concepts as transference, which might be treated in Money's frame of reference as encoded perceptual or conceptual material, are rather conspicuously omitted, even if only to be rejected. A theoretical synopsis is provided. A supernumerary appendix is included on some ideas concerning suffixes and psychological verbiage. One intriguing, and doubtless jocose, statement arising out of this peregrination is that "motivation is patrician."

All in all, the book seems to tend toward, but not quite reach, new formulations, except in scattered and relatively undeveloped snatches. It, in many ways, subtly mimes the theoretical formulation of classical analytic psychology. This, again, demonstrates either the primacy and appositeness of the analytic frame of reference, or the inability of the modern-day intellectual and searching mind to escape the centripetal forces of a relatively closed and, to many, satisfying frame of reference. One is perhaps reminded of the remark of the first of the Ming emperors, as quoted by Y. Y. Chen, who said, when he had achieved the completion of the examination form for the Chinese scholar: "Now I will have all the intellectuals in my trap." Satisfaction with an encompassing system is, of course, not tantamount to validation of that system.

JORDAN M. SCHER, M.D.

Psychotherapy by Reciprocal Inhibition. By Joseph Wolpe, M.D. Price, $5.00. Pp. 239. Stanford University Press, Stanford, Calif., 1958.

There is, perhaps, no more devastating way to review a book than to quote passages from it that sound uninformed or doctrinaire out of their qualifying context. However, Dr. Wolpe himself insists that the following are his essential theses:

Experimental Basis of His Work

(Pp. ix-x) "Only three kinds of processes are known that can bring about lasting changes in an organism's habit of response to a given stimulus situation: growth, lesions, and learning. Since neurotic behavior demonstrably originates in learning, it is only to be expected that its elimination will be a matter of 'unlearning.' . . .

"The experimental observations came first. They were made on cats in which lasting neurotic states had been induced by the administration of several punishing but nondamaging shocks in a small cage. The neurotic anxiety and other reactions were subsequently in every case entirely removed by getting the animals to eat in the presence of small, and at later sessions progressively larger, 'doses' of anxiety-evoking stimuli. . . .

"The suggestion that arose from these experiments was that human neurotic anxieties might similarly be handled by opposing feeding behavior to them."

Implications with Regard to Human Behavior

(P. 19) "Man himself has probably no maturationally established stimulus-response sequences that are complex enough to be called instinctive."

(Pp. 32-33) "Neurotic behavior is any persistent habit of unadaptive behavior acquired by learning in a physiologically normal organism. . . .

"Much has been made of the concept of 'secondary gain,' and it has led to the absurd idea that patients *want* their neuroses. The truth is that human beings are the unfortunate recipients of neurotic conditioning, just as animals may be; and I have never seen one who felt, when he was cured, that something valuable had been taken away from him."

Clinical Applications

(P. xi) "Details will be found in the body of the book, but here is an outline of one of the more important techniques. In this, relaxation is used to counter the effects of anxiety-evoking stimuli; paralleling in an obvious way the method of therapy in animals, described above. The patient is given preliminary training in relaxation by Jacobson's method (1938). Meanwhile an 'anxiety hierarchy' is constructed. This is a list of stimuli to which the patient reacts with maladaptive anxiety. The items are ranked according to the amount of disturbance they cause, the most disturbing items being placed at the top and the least at the bottom. The patient is hypnotized and made to relax as deeply as possible. Then he is told to imagine the weakest item in the anxiety hierarchy—the smallest 'dose' of phobic stimulation. If the relaxation is unimpaired by this, a slightly greater 'dose' is presented at the next session. The 'dosage' is gradually increased from session to session, until at last the phobic stimulus can be presented at maximum intensity without impairing the calm, relaxed state. It will then be found that the patient has ceased to react with his previous anxiety to encounters in real life with even the strongest of the once phobic stimuli. . . . Of course, my patients, too, profit from these nonspecific effects of the interview situation; but that *my* special methods *do* have an additional effect is suggested by a ratio of 'apparently cured' and 'much improved' patients that is consistently in the region of 90 per cent."

Typical Ancillary Therapy

(P. 200) "Thought Stopping: The patient is asked to shut his eyes and to verbalize a typical maladaptive thought sequence. Suddenly the therapist shouts, 'Stop!' All this is repeated several times, and attention is drawn to the fact that the thoughts actually do stop each time. The patient is then told that he himself can stop his thoughts equally successfully by saying 'stop' subvocally. The thoughts of course soon return, but after repeated stopping, they return less readily and become progressively easier to stop. With assiduous practice some patients become largely or entirely free of these futile thoughts within a week or so."

Evaluation of Results

(P. 220) "The Present Status of Reciprocal Inhibition as the Main Basis of Fundamental Therapy of Human Neuroses:

"The following are some major facts that support the hypothesis that reciprocal inhibition has a central role in human psychotherapy:

"1. In general, it is possible to overcome a habit by forming a new and antagonistic habit in the same stimulus situation.

"2. Animal neuroses are overcome if feeding can be made to occur in the presence of anxiety-evoking stimuli. Under other conditions anxiety inhibits feeding, and presenting anxiety-evoking stimuli in special circumstances can lead to the conditioning of anxiety to food-approach stimuli.

"3. By deliberately applying responses antagonistic to anxiety responses, neurotic anxiety-response habits can be overcome, and more neurotic patients can be successfully treated, apparently, than by other methods.

"4. The success of other approaches to therapy is explicable on the reciprocal inhibition principle.

"5. 'Spontaneous' improvement of neuroses in the ordinary course of life is explicable on the reciprocal inhibition principle.

"It is obvious that if the reciprocal inhibition principle is indeed a master key to the cure of neurosis, a much brighter future lies before the world's victims of neurotic suffering."

From this representative sampling the reader may form his own conclusions as to whether he desires further acquaintance with this volume.

Jules H. Masserman, M.D.

The Door of Serenity: A Study in the Therapeutic Use of Symbolic Painting. By Ainslie Meares. Price, $4.50. Pp. 119, with 24 colored plates. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Dr. Meares is a distinguished Australian psychiatrist who has written a number of books concerned with hypnotic painting and studies of interpersonal reactions. In this volume he

reports a study in the therapeutic use of symbolic painting applied to a single seriously ill schizophrenic young woman. It is a beautifully written book, full of the author's sincere empathy for a patient who communicated to him through the medium of her paintings. The first painting represents the patient's chaos. It was bizarre, weird, and horrible, complete with darkness and eyes of people looking at her. It represented her complete disorganization and chaos. The last painting, as the patient became calm, serene, and almost well, is a beautiful picture of a bird free to fly in the air. After this last painting the patient painted no more but continued her therapy in interviews with verbal communications. The story ends with the patient well and on a trip across the world, touring by herself and writing factual letters about the great galleries of the Old World, even with a touch of humor.

How was this result accomplished? Not by intellectual insight achieved through verbal communications, but by messages conveyed from the patient to the therapist, who tried hard to understand. The painful process that he went through is clearly delineated at periods when he felt that the patient might destroy herself. Here he was in trouble, not knowing whether to institutionalize her or to continue therapy with a calculated risk. The mutual effort at understanding with Dr. Meares' empathy and sincerity must have accomplished some internal reorganization of the patient's personality. However, this was not an intellectual understanding that the patient achieved, although the author says: "I think that she has great understanding. It is the understanding of those whose minds have been burnished in the fire of insanity and who have come through the ordeal." Yet Dr. Meares recognizes that the understanding is of a different order than that which we usually denote by the term, for in the last paragraph he admonishes the patient: "If you should happen to come upon this book and read it, remember this—there is nothing in it that you do not already know. Remember this, and it will not disturb you. It is merely a glimpse of the great ordeal which has made you what you are—a person of great insight and sensitivity."

The artistry of the patient is well matched by the poetry of the author. To appreciate fully at least one way of treating a schizophrenic, this book is recommended to all those who are interested in working hard to achieve a successful result in these very severely ill patients.

ROY R. GRINKER, M.D.

The Clinical Application of Projective Drawings. By Emanuel F. Hammer, Editor. Price, $13.50. Pp. 688. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

This 688 page book fills a much-needed gap in presenting a comprehensive survey of drawing techniques used to study personality. To this point, there have existed only a few creditable publications on specific drawing tests, or superficial chapters in books surveying the projective techniques. In presenting the basic technique of Machover's Draw-A-Person Test and numerous variants of it, plus illustrations of their applications, Hammer has added substantially to the status of the drawing technique as a clinical tool.

Author-editor Hammer calls his book "clinical," in the sense that it is aimed at "the practicing clinician and the clinician-in-training." One of the main purposes of the book is to demonstrate the usefulness of this projective technique as an economical diagnostic method in actual practice and as an adjunct to psychotherapy. In general, this purpose is accomplished.

Hammer's collaborators include the foremost authorities in the field of drawing techniques and allied projective instruments, writing on their specialties. Included are John Buck (exponent of the House-Tree-Person Test); Molly Harrower (The Most Unpleasant Concept Test); Marian G. Kinget, who reviews Wartegg's unique Drawing Completion Test; Edwin Shneidman, discussing relationship between thematic and drawing materials; Margaret Naumberg, on Art Therapy; Sidney Levy, on animal drawings, and Hammer, who discussed other variants of the Draw-A-Person Test, such as Draw-A-Family, Draw-A-Person in the Rain, the Rosenberg Draw-A-Person Test, which makes use of carbon copies, and the Eight-Card Redrawing Test. Even doodles are discussed! In addition, Lauretta Bender, Florence Halpern, Isaac Jolles, Karen Machover, Paul Schilder, and others show applications of the drawing techniques in a variety of concise case studies. Included in the case studies are pre- and post-therapy comparisons of drawings.

There are also detailed sections of the expressive aspects of projective drawings, including some not too well-documented criteria for interpretations. A section on research faces the problem of validity and reliability, but the shortcomings of this youthful (20-year-old) technique are reflected by the frequently unverified interpretations made by some of the con-

tributors, especially Hammer. To this reviewer it seems that too many of the drawing analyses represent only so faithfully the astute observation made by Gordon Allport and cited by Hammer: "The greatest failing of the psychologist at the present time is his inability to prove what he knows to be true." Many correlative statements of something-standing-for-something-else were noted, and the sophisticated reader should evaluate their validity with more caution than is exercised by the writers who made such statements. It seemed that sheer quantity ("... in 5500 drawings ...") and personal experience too often were substituted uncritically for reasoned interpretations based on existing research or theory.

In spite of this rather serious flaw (which several of the contributors did not commit), the book is otherwise well written, at times with flowery phraseology, and excellently documented as to original studies. As a reference source it brings up-to-date much of the relevant literature and will be of use to those contemplating research in this area. The material is well organized; the index is good. There are numerous drawings illustrating the raw data. Many of the drawings are quite dramatic. It is too bad that the editor did not see fit to sacrifice the expensive glossy pages in order to publish the chromatic drawings in color.

The case studies are comprehensive in a scope and illustrate well the usefulness of the drawing technique as a diagnostic tool. Also, its value as an index of psychotherapeutic progress is adequately demonstrated. It is interesting to compare the various approaches used by the contributors of case material. This reviewer was rather concerned at the analyses forwarded by Buck. His interpretations seemed highly idiosyncratic and lacking in empirical verification, or even theoretical relevance. Hammer leans heavily to Buck's work and commits similar errors in interpretive thinking.

Lack of theory is another shortcoming of the book. In spite of the clinical orientation of the book, a technique which has barely passed the infant stage of development needs the structure of theoretical formulations. The theoretical offerings of the book are considered meager. For example, there is proportionately little discussion given to the mechanisms of defense in relation to drawings. Another limitation is that there are too few data cited for nonclinical groups.

The section of formal scoring and interpretation is comprehensive in scope but will not be very helpful to the novice. Although qualitatively rich in presenting an array of signs and symbols, it does not provide a quantified schema by which to assess the multidimensionality of personality as captured on paper by drawings. Admittedly, few techniques accomplish this important but complex task.

Perhaps a book like this must have such shortcomings, and, hopefully, further research will be thereby stimulated to put the Draw-A-Person Test more firmly on its feet as a diagnostic instrument. Hammer admits that this book is "not yet the full-dress debut of a wholly mature scientific instrument."

Over-all, the book can be recommended to students and practitioners in psychiatry and psychology as a useful reference source about projective drawings, and successive revisions will perhaps reveal the further growth of this unique clinical technique.

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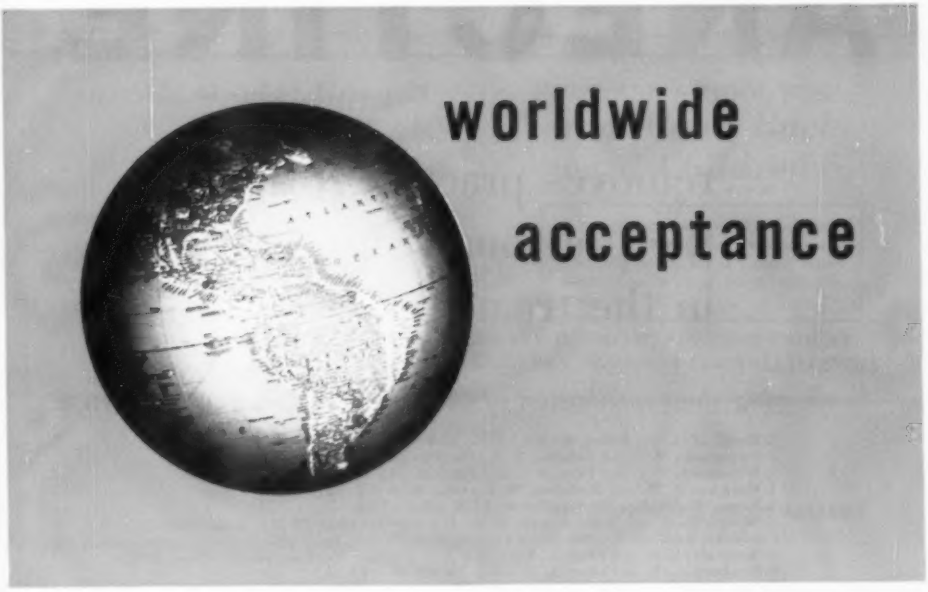

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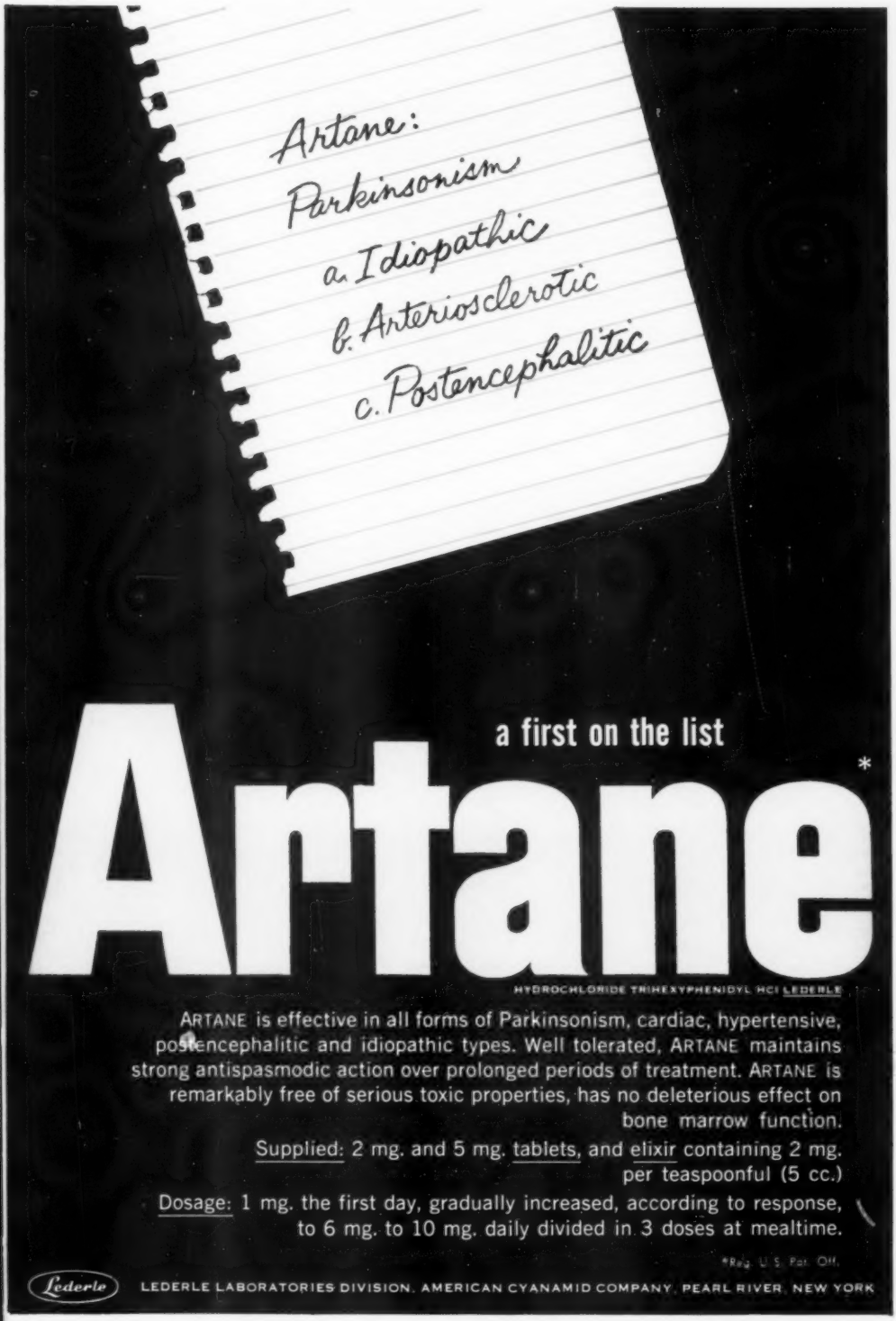
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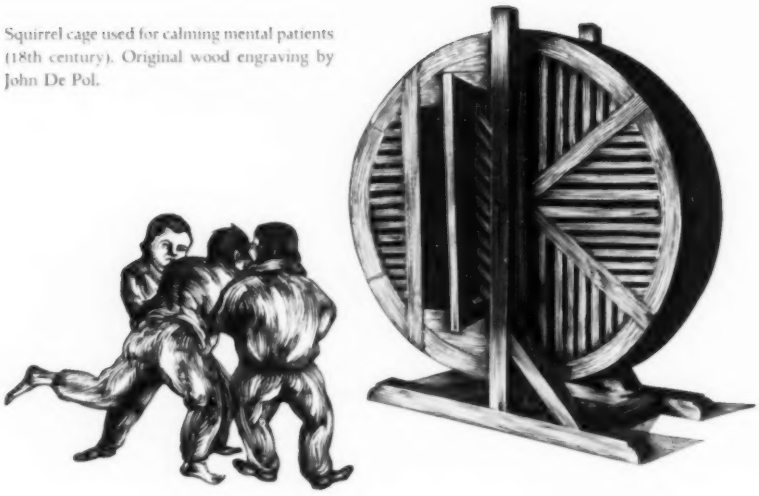

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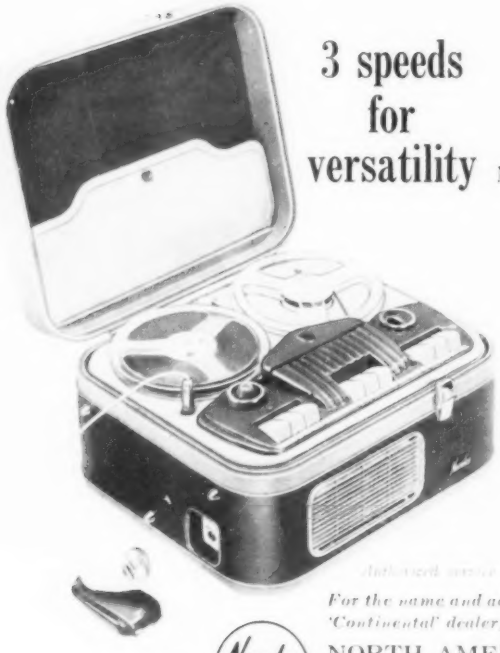

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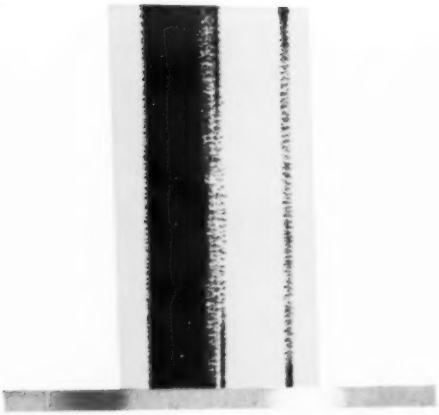

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